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- (71) Applicant (*for all designated States except US*): GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): WU, Thomas, D. [US/US]; 41 Nevada Street, San Francisco, CA 94110 (US). ZHANG, Zemin [US/US]; 876 Taurus Drive, Foster City, CA 94404 (US). ZHOU, Yan [CN/US]; #111, 525 N Curtis Avenue, Alhambra, CA 91801 (US).
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(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF TUMOR

(57) Abstract: The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using those compositions of matter for the same.

## COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF TUMOR

FIELD OF THE INVENTION

The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using those compositions of matter for the same.

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BACKGROUND OF THE INVENTION

Malignant tumors (cancers) are the second leading cause of death in the United States, after heart disease (Boring et al., *CA Cancer J. Clin.* 43:7 (1993)). Cancer is characterized by the increase in the number of abnormal, or neoplastic, cells derived from a normal tissue which proliferate to form a tumor mass, the invasion of adjacent tissues by these neoplastic tumor cells, and the generation of malignant cells which eventually spread via the blood or lymphatic system to regional lymph nodes and to distant sites via a process called metastasis. In a cancerous state, a cell proliferates under conditions in which normal cells would not grow. Cancer manifests itself in a wide variety of forms, characterized by different degrees of invasiveness and aggressiveness.

15 In attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify transmembrane or otherwise membrane-associated polypeptides that are specifically expressed on the surface of one or more particular type(s) of cancer cell as compared to on one or more normal non-cancerous cell(s). Often, such membrane-associated polypeptides are more abundantly expressed on the surface of the cancer cells as compared to on the surface of the non-cancerous cells. The identification of such tumor-associated cell surface antigen polypeptides has given rise to the ability to specifically target cancer cells for destruction via antibody-based therapies. In this regard, it is noted that antibody-based therapy has proved very effective in the treatment of certain cancers. For example, HERCEPTIN® and RITUXAN® (both from Genentech Inc., South San Francisco, California) are antibodies that have been used successfully to treat breast cancer and non-Hodgkin's lymphoma, respectively. More specifically, HERCEPTIN® is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) proto-oncogene. HER2 protein overexpression is observed in 25-30% of primary breast cancers. RITUXAN® is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Both these antibodies are recombinantly produced in CHO cells.

25  
30 In other attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify (1) non-membrane-associated polypeptides that are specifically produced by one or more particular type(s) of cancer cell(s) as compared to by one or more particular type(s) of non-cancerous normal cell(s), (2) polypeptides that are produced by cancer cells at an expression level that is significantly higher than that of one or more normal non-cancerous cell(s), or (3) polypeptides whose expression is specifically limited



to only a single (or very limited number of different) tissue type(s) in both the cancerous and non-cancerous state (e.g., normal prostate and prostate tumor tissue). Such polypeptides may remain intracellularly located or may be secreted by the cancer cell. Moreover, such polypeptides may be expressed not by the cancer cell itself, but rather by cells which produce and/or secrete polypeptides having a potentiating or growth-enhancing effect on cancer cells. Such secreted polypeptides are often proteins that provide cancer cells with a growth advantage over normal cells and include such things as, for example, angiogenic factors, cellular adhesion factors, growth factors, and the like. Identification of antagonists of such non-membrane associated polypeptides would be expected to serve as effective therapeutic agents for the treatment of such cancers. Furthermore, identification of the expression pattern of such polypeptides would be useful for the diagnosis of particular cancers in mammals.

Despite the above identified advances in mammalian cancer therapy, there is a great need for additional diagnostic and therapeutic agents capable of detecting the presence of tumor in a mammal and for effectively inhibiting neoplastic cell growth, respectively. Accordingly, it is an objective of the present invention to identify: (1) cell membrane-associated polypeptides that are more abundantly expressed on one or more type(s) of cancer cell(s) as compared to on normal cells or on other different cancer cells, (2) non-membrane-associated polypeptides that are specifically produced by one or more particular type(s) of cancer cell(s) (or by other cells that produce polypeptides having a potentiating effect on the growth of cancer cells) as compared to by one or more particular type(s) of non-cancerous normal cell(s), (3) non-membrane-associated polypeptides that are produced by cancer cells at an expression level that is significantly higher than that of one or more normal non-cancerous cell(s), or (4) polypeptides whose expression is specifically limited to only a single (or very limited number of different) tissue type(s) in both a cancerous and non-cancerous state (e.g., normal prostate and prostate tumor tissue), and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of cancer in mammals. It is also an objective of the present invention to identify cell membrane-associated, secreted or intracellular polypeptides whose expression is limited to a single or very limited number of tissues, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of cancer in mammals.

## SUMMARY OF THE INVENTION

### A. Embodiments

In the present specification, Applicants describe for the first time the identification of various cellular polypeptides (and their encoding nucleic acids or fragments thereof) which are expressed to a greater degree on the surface of or by one or more types of cancer cell(s) as compared to on the surface of or by one or more types of normal non-cancer cells. Alternatively, such polypeptides are expressed by cells which produce and/or secrete polypeptides having a potentiating or growth-enhancing effect on cancer cells. Again alternatively, such polypeptides may not be overexpressed by tumor cells as compared to normal cells of the same tissue type, but rather may be specifically expressed by both tumor cells and normal cells of only a single or very limited

number of tissue types (preferably tissues which are not essential for life, e.g., prostate, etc.). All of the above polypeptides are herein referred to as Tumor-associated Antigenic Target polypeptides ("TAT" polypeptides) and are expected to serve as effective targets for cancer therapy and diagnosis in mammals.

Accordingly, in one embodiment of the present invention, the invention provides an isolated nucleic acid molecule having a nucleotide sequence that encodes a tumor-associated antigenic target polypeptide or fragment thereof (a "TAT" polypeptide).

In certain aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule encoding a full-length TAT polypeptide having an amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule comprising the coding sequence of a full-length TAT polypeptide cDNA as disclosed herein, the coding sequence of a TAT polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In further aspects, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule that encodes the same mature polypeptide encoded by the full-length coding region of any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect of the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a TAT polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide(s) are disclosed herein. Therefore, soluble extracellular domains of the herein described TAT polypeptides are contemplated.

In other aspects, the present invention is directed to isolated nucleic acid molecules which hybridize to (a) a nucleotide sequence encoding a TAT polypeptide having a full-length amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular

domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the nucleotide sequence of (a). In this regard, an embodiment of the present invention is directed to fragments of a full-length TAT polypeptide coding sequence, or the complement thereof, as disclosed herein, that may find use as, for example, hybridization probes useful as, for example, diagnostic probes, antisense oligonucleotide probes, or for encoding fragments of a full-length TAT polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-TAT polypeptide antibody, a TAT binding oligopeptide or other small organic molecule that binds to a TAT polypeptide. Such nucleic acid fragments are usually at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a TAT polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the TAT polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which TAT polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such novel fragments of TAT polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the TAT polypeptide fragments encoded by these nucleotide molecule fragments, preferably those TAT polypeptide fragments that comprise a binding site for an anti-TAT antibody, a TAT binding oligopeptide or other small organic molecule that binds to a TAT polypeptide.

In another embodiment, the invention provides isolated TAT polypeptides encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated TAT polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity, to a TAT polypeptide having a full-length amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide protein, with or without the signal peptide, as disclosed herein, an amino acid sequence encoded by any of the nucleic acid sequences disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated TAT polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid

sequence identity, to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated TAT polypeptide without the N-terminal signal sequence and/or without the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the TAT polypeptide and recovering the TAT polypeptide from the cell culture.

Another aspect of the invention provides an isolated TAT polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the TAT polypeptide and recovering the TAT polypeptide from the cell culture.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides isolated chimeric polypeptides comprising any of the herein described TAT polypeptides fused to a heterologous (non-TAT) polypeptide. Example of such chimeric molecules comprise any of the herein described TAT polypeptides fused to a heterologous polypeptide such as, for example, an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, single-chain antibody or antibody that competitively inhibits the binding of an anti-TAT polypeptide antibody to its respective antigenic epitope. Antibodies of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which they bind. For diagnostic purposes, the antibodies of the present invention may be detectably labeled, attached to a solid support, or the like.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described antibodies. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described antibodies is further provided and comprises culturing host cells under conditions suitable for expression of the desired antibody and recovering the desired antibody from the cell culture.

In another embodiment, the invention provides oligopeptides ("TAT binding oligopeptides") which

bind, preferably specifically, to any of the above or below described TAT polypeptides. Optionally, the TAT binding oligopeptides of the present invention may be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The TAT binding oligopeptides of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which they bind. For diagnostic purposes, the TAT binding oligopeptides of the present invention may be detectably labeled, attached to a solid support, or the like.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described TAT binding oligopeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described TAT binding oligopeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired oligopeptide and recovering the desired oligopeptide from the cell culture.

In another embodiment, the invention provides small organic molecules ("TAT binding organic molecules") which bind, preferably specifically, to any of the above or below described TAT polypeptides. Optionally, the TAT binding organic molecules of the present invention may be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The TAT binding organic molecules of the present invention preferably induce death of a cell to which they bind. For diagnostic purposes, the TAT binding organic molecules of the present invention may be detectably labeled, attached to a solid support, or the like.

In a still further embodiment, the invention concerns a composition of matter comprising a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

In yet another embodiment, the invention concerns an article of manufacture comprising a container and a composition of matter contained within the container, wherein the composition of matter may comprise a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein. The article may further optionally comprise a label affixed to the container, or a package insert included with the container, that refers to the use of the composition of matter for the therapeutic treatment or diagnostic detection of a tumor.

Another embodiment of the present invention is directed to the use of a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT polypeptide antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein, for the preparation of a medicament useful in the treatment of a condition which is responsive to the TAT polypeptide, chimeric TAT polypeptide, anti-TAT polypeptide antibody, TAT binding oligopeptide, or TAT

binding organic molecule.

B. Additional Embodiments

Another embodiment of the present invention is directed to a method for inhibiting the growth of a cell that expresses a TAT polypeptide, wherein the method comprises contacting the cell with an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, and wherein the binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide causes inhibition of the growth of the cell expressing the TAT polypeptide. In preferred embodiments, the cell is a cancer cell and binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide causes death of the cell expressing the TAT polypeptide. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and TAT binding oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet another embodiment of the present invention is directed to a method of therapeutically treating a mammal having a cancerous tumor comprising cells that express a TAT polypeptide, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby resulting in the effective therapeutic treatment of the tumor. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet another embodiment of the present invention is directed to a method of determining the presence of a TAT polypeptide in a sample suspected of containing the TAT polypeptide, wherein the method comprises exposing the sample to an antibody, oligopeptide or small organic molecule that binds to the TAT polypeptide and determining binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide in the sample, wherein the presence of such binding is indicative of the presence of the TAT polypeptide in the sample. Optionally, the sample may contain cells (which may be cancer cells) suspected of expressing the TAT polypeptide. The antibody, TAT binding oligopeptide or TAT binding organic molecule employed in the method may optionally be detectably labeled, attached to a solid support, or the like.

A further embodiment of the present invention is directed to a method of diagnosing the presence of a tumor in a mammal, wherein the method comprises detecting the level of expression of a gene encoding a TAT polypeptide (a) in a test sample of tissue cells obtained from said mammal, and (b) in a control sample of known normal non-cancerous cells of the same tissue origin or type, wherein a higher level of expression of the

TAT polypeptide in the test sample, as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test sample was obtained.

Another embodiment of the present invention is directed to a method of diagnosing the presence of a tumor in a mammal, wherein the method comprises (a) contacting a test sample comprising tissue cells obtained from the mammal with an antibody, oligopeptide or small organic molecule that binds to a TAT polypeptide and  
5 (b) detecting the formation of a complex between the antibody, oligopeptide or small organic molecule and the TAT polypeptide in the test sample, wherein the formation of a complex is indicative of the presence of a tumor in the mammal. Optionally, the antibody, TAT binding oligopeptide or TAT binding organic molecule employed is detectably labeled, attached to a solid support, or the like, and/or the test sample of tissue cells is obtained from an individual suspected of having a cancerous tumor.

10 Yet another embodiment of the present invention is directed to a method for treating or preventing a cell proliferative disorder associated with altered, preferably increased, expression or activity of a TAT polypeptide, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a TAT polypeptide. Preferably, the cell proliferative disorder is cancer and the antagonist of the TAT polypeptide is an anti-TAT polypeptide antibody, TAT binding oligopeptide, TAT binding organic  
15 molecule or antisense oligonucleotide. Effective treatment or prevention of the cell proliferative disorder may be a result of direct killing or growth inhibition of cells that express a TAT polypeptide or by antagonizing the cell growth potentiating activity of a TAT polypeptide.

Yet another embodiment of the present invention is directed to a method of binding an antibody, oligopeptide or small organic molecule to a cell that expresses a TAT polypeptide, wherein the method  
20 comprises contacting a cell that expresses a TAT polypeptide with said antibody, oligopeptide or small organic molecule under conditions which are suitable for binding of the antibody, oligopeptide or small organic molecule to said TAT polypeptide and allowing binding therebetween.

Other embodiments of the present invention are directed to the use of (a) a TAT polypeptide, (b) a nucleic acid encoding a TAT polypeptide or a vector or host cell comprising that nucleic acid, (c) an anti-TAT  
25 polypeptide antibody, (d) a TAT-binding oligopeptide, or (e) a TAT-binding small organic molecule in the preparation of a medicament useful for (i) the therapeutic treatment or diagnostic detection of a cancer or tumor, or (ii) the therapeutic treatment or prevention of a cell proliferative disorder.

Another embodiment of the present invention is directed to a method for inhibiting the growth of a cancer cell, wherein the growth of said cancer cell is at least in part dependent upon the growth potentiating  
30 effect(s) of a TAT polypeptide (wherein the TAT polypeptide may be expressed either by the cancer cell itself or a cell that produces polypeptide(s) that have a growth potentiating effect on cancer cells), wherein the method comprises contacting the TAT polypeptide with an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby antagonizing the growth-potentiating activity of the TAT polypeptide and, in turn, inhibiting the growth of the cancer cell. Preferably the growth of the cancer cell is completely inhibited.  
35 Even more preferably, binding of the antibody, oligopeptide or small organic molecule to the TAT polypeptide induces the death of the cancer cell. Optionally, the antibody is a monoclonal antibody, antibody fragment,

chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and TAT binding oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet another embodiment of the present invention is directed to a method of therapeutically treating a tumor in a mammal, wherein the growth of said tumor is at least in part dependent upon the growth potentiating effect(s) of a TAT polypeptide, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby antagonizing the growth potentiating activity of said TAT polypeptide and resulting in the effective therapeutic treatment of the tumor. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet further embodiments of the present invention will be evident to the skilled artisan upon a reading of the present specification.

#### BRIEF DESCRIPTION OF THE DRAWINGS

In the list of figures for the present application, specific cDNA sequences which are upregulated in certain tumor tissues as compared to their normal tissue counterparts are individually identified with a designation beginning with the letters "DNA" followed by a specific numerical designation. A full or partial length protein sequence that is encoded by a cDNA sequence identified and shown herein is individually identified with a designation beginning with the letters "PRO" followed by a specific numerical designation. Figures showing encoded amino acid sequences immediately follow the figure showing the cDNA sequence encoding that specific amino acid sequence. If start and/or stop codons have been identified in a cDNA sequence shown in the attached figures, they are shown in bold and underlined font.



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 Figure 44: DNA151148, NM\_004781, gen.NM\_004781  
 Figure 45: PRO12618  
 Figure 46: DNA323740, XM\_086151, gen.XM\_086151  
 Figure 47: PRO80497  
 Figure 48: DNA171408, NM\_004401, gen.NM\_004401  
 Figure 49: PRO20136  
 Figure 50: DNA323741, NM\_003132, gen.NM\_003132  
 Figure 51: PRO80498  
 Figure 52: DNA323742, XM\_086586, gen.XM\_086586  
 Figure 53: PRO80499  
 Figure 54: DNA323743, XM\_086587, gen.XM\_086587  
 Figure 55: DNA323744, XM\_059230, gen.XM\_059230  
 Figure 56: PRO80501  
 Figure 57A-B: DNA323745, XM\_048780, gen.XM\_048780  
 Figure 58: DNA323746, XM\_053183, gen.XM\_053183  
 Figure 59: DNA323747, XM\_165442, gen.XM\_165442  
 Figure 60: DNA323748, NM\_033440, gen.NM\_033440  
 Figure 61: PRO2269  
 Figure 62: DNA323749, NM\_024329, gen.NM\_024329  
 Figure 63: PRO80505  
 Figure 64: DNA323750, XM\_018205, gen.XM\_018205  
 Figure 65: PRO80506  
 Figure 66: DNA323751, XM\_011650, gen.XM\_011650  
 Figure 67: DNA323752, XM\_017315, gen.XM\_017315  
 Figure 68A-B: DNA323753, XM\_030470, gen.XM\_030470  
 Figure 69: DNA323754, NM\_004930, gen.NM\_004930  
 Figure 70: PRO80510  
 Figure 71: DNA323755, NM\_003689, gen.NM\_003689  
 Figure 72: PRO80511  
 Figure 73: DNA323756, NM\_016183, gen.NM\_016183  
 Figure 74: PRO80512  
 Figure 75: DNA323757, XM\_015234, gen.XM\_015234  
 Figure 76A-B: DNA323758, XM\_027916, gen.XM\_027916  
 Figure 77: DNA323759, XM\_033683, gen.XM\_033683  
 Figure 78: DNA323760, XM\_001826, gen.XM\_001826  
 Figure 79: DNA323761, XM\_033654, gen.XM\_033654  
 Figure 80: PRO80517  
 Figure 81: DNA323762, NM\_001791, gen.NM\_001791  
 Figure 82: PRO26194  
 Figure 83: DNA323763, NM\_005826, gen.NM\_005826  
 Figure 84: PRO60815  
 Figure 85: DNA323764, XM\_086357, gen.XM\_086357  
 Figure 86: PRO80518  
 Figure 87: DNA323765, NM\_000975, gen.NM\_000975  
 Figure 88: PRO80519  
 Figure 89: DNA323766, NM\_007260, gen.NM\_007260  
 Figure 90: PRO61250  
 Figure 91: DNA323767, NM\_017761, gen.NM\_017761  
 Figure 92: PRO80520  
 Figure 93: DNA323768, NM\_006625, gen.NM\_006625  
 Figure 94: PRO22196  
 Figure 95: DNA323769, NM\_054016, gen.NM\_054016  
 Figure 96: PRO80521  
 Figure 97: DNA323770, XM\_086375, gen.XM\_086375  
 Figure 98: DNA323771, XM\_006290, gen.XM\_006290  
 Figure 99: DNA323772, NM\_015484, gen.NM\_015484  
 Figure 100: PRO80524  
 Figure 101A-B: DNA323773, XM\_001616, gen.XM\_001616  
 Figure 102: DNA323774, XM\_058240,

gen.XM\_058240  
Figure 103: DNA323775, XM\_059117,  
gen.XM\_059117  
Figure 104: PRO80527  
Figure 105: DNA226262, NM\_005563,  
gen.NM\_005563  
Figure 106: PRO36725  
Figure 107: DNA323776, NM\_022778,  
gen.NM\_022778  
Figure 108: PRO80528  
Figure 109: DNA323777, XM\_017846,  
gen.XM\_017846  
Figure 110: DNA323778, NM\_005517,  
gen.NM\_005517  
Figure 111: PRO80530  
Figure 112A-C: DNA323779, XM\_046918,  
gen.XM\_046918  
Figure 113: DNA323780, XM\_002114,  
gen.XM\_002114  
Figure 114: DNA323781, XM\_059066,  
gen.XM\_059066  
Figure 115: PRO80533  
Figure 116: DNA323782, NM\_018066,  
gen.NM\_018066  
Figure 117: PRO80534  
Figure 118: DNA323783, NM\_006600,  
gen.NM\_006600  
Figure 119: PRO80535  
Figure 120: DNA323784, XM\_059067,  
gen.XM\_059067  
Figure 121: PRO80536  
Figure 122: DNA323785, NM\_032872,  
gen.NM\_032872  
Figure 123: PRO80537  
Figure 124: DNA196349, NM\_006990,  
gen.NM\_006990  
Figure 125: PRO24856  
Figure 126: DNA323788, XM\_001640,  
gen.XM\_001640  
Figure 127: DNA323789, NM\_002946,  
gen.NM\_002946  
Figure 128: PRO59099  
Figure 129: DNA323790, XM\_114044,  
gen.XM\_114044  
Figure 130: DNA323791, XM\_059088,  
gen.XM\_059088  
Figure 131: DNA323792, NM\_031459,  
gen.NM\_031459  
Figure 132: PRO80542  
Figure 133: DNA323793, XM\_010664,  
gen.XM\_010664  
Figure 134: DNA323794, XM\_001812,  
gen.XM\_001812  
Figure 135: DNA323795, XM\_001807,  
gen.XM\_001807  
Figure 136: DNA323796, XM\_086444,

gen.XM\_086444  
Figure 137: DNA323797, NM\_024640,  
gen.NM\_024640  
Figure 138: PRO80547  
Figure 139A-B: DNA323798, XM\_049310,  
gen.XM\_049310  
Figure 140: DNA323799, XM\_113374,  
gen.XM\_113374  
Figure 141: DNA323800, XM\_002105,  
gen.XM\_002105  
Figure 142: DNA323801, NM\_014571,  
gen.NM\_014571  
Figure 143: PRO80550  
Figure 144: DNA323802, XM\_165438,  
gen.XM\_165438  
Figure 145: DNA323803, XM\_029844,  
gen.XM\_029844  
Figure 146: DNA188748, NM\_006559,  
gen.NM\_006559  
Figure 147: PRO22304  
Figure 148: DNA323804, NM\_003757,  
gen.NM\_003757  
Figure 149: PRO80553  
Figure 150: DNA323805, NM\_004964,  
gen.NM\_004964  
Figure 151: PRO80554  
Figure 152: DNA323806, NM\_023009,  
gen.NM\_023009  
Figure 153: PRO80555  
Figure 154: DNA323807, XM\_030423,  
gen.XM\_030423  
Figure 155A-B: DNA323808, XM\_036299,  
gen.XM\_036299  
Figure 156: PRO80557  
Figure 157: DNA227213, NM\_003680,  
gen.NM\_003680  
Figure 158: PRO37676  
Figure 159: DNA323809, NM\_006112,  
gen.NM\_006112  
Figure 160: PRO80558  
Figure 161: DNA323810, XM\_018136,  
gen.XM\_018136  
Figure 162: PRO80559  
Figure 163: DNA323811, XM\_117184,  
gen.XM\_117184  
Figure 164: PRO80560  
Figure 165: DNA323812, NM\_017825,  
gen.NM\_017825  
Figure 166: PRO80561  
Figure 167: DNA189315, NM\_014408,  
gen.NM\_014408  
Figure 168: PRO22262  
Figure 169A-B: DNA323813, XM\_029031,  
gen.XM\_029031  
Figure 170: PRO80562  
Figure 171: DNA323814, XM\_059171,

gen.XM\_059171  
 Figure 172: PRO80563  
 Figure 173: DNA83085, NM\_000760, gen.NM\_000760  
 Figure 174: PRO2583  
 Figure 175: DNA323815, XM\_165984, gen.XM\_165984  
 Figure 176: DNA323816, XM\_029842, gen.XM\_029842  
 Figure 177: PRO2851  
 Figure 178: DNA323817, XM\_086384, gen.XM\_086384  
 Figure 179: PRO80565  
 Figure 180A-C: DNA274487, NM\_014747, gen.NM\_014747  
 Figure 181: PRO62389  
 Figure 182: DNA323818, XM\_010712, gen.XM\_010712  
 Figure 183: DNA323819, NM\_024664, gen.NM\_024664  
 Figure 184: PRO80567  
 Figure 185: DNA323820, XM\_059214, gen.XM\_059214  
 Figure 186: PRO80568  
 Figure 187: DNA323821, XM\_046349, gen.XM\_046349  
 Figure 188: DNA103253, NM\_006516, gen.NM\_006516  
 Figure 189: PRO4583  
 Figure 190: DNA323822, XM\_086543, gen.XM\_086543  
 Figure 191: PRO80570  
 Figure 192: DNA274745, NM\_006824, gen.NM\_006824  
 Figure 193: PRO62518  
 Figure 194: DNA273060, NM\_001255, gen.NM\_001255  
 Figure 195: PRO61125  
 Figure 196: DNA323823, NM\_030587, gen.NM\_030587  
 Figure 197: PRO80571  
 Figure 198: DNA323824, XM\_097649, gen.XM\_097649  
 Figure 199: DNA256503, NM\_003780, gen.NM\_003780  
 Figure 200: PRO51539  
 Figure 201: DNA323825, XM\_046450, gen.XM\_046450  
 Figure 202A-B: DNA272024, NM\_014663, gen.NM\_014663  
 Figure 203: PRO60298  
 Figure 204: DNA323826, XM\_046565, gen.XM\_046565  
 Figure 205: PRO80574  
 Figure 206: DNA323827, NM\_024602, gen.NM\_024602  
 Figure 207: PRO80575  
 Figure 208: DNA323828, XM\_046557, gen.XM\_046557  
 Figure 209: PRO80576  
 Figure 210: DNA323829, NM\_001012, gen.NM\_001012  
 Figure 211: PRO10760  
 Figure 212: DNA323830, XM\_046551, gen.XM\_046551  
 Figure 213A-B: DNA323831, XM\_027983, gen.XM\_027983  
 Figure 214: DNA323832, XM\_086324, gen.XM\_086324  
 Figure 215: PRO80579  
 Figure 216: DNA323833, XM\_032391, gen.XM\_032391  
 Figure 217: PRO80580  
 Figure 218: DNA103214, NM\_006066, gen.NM\_006066  
 Figure 219: PRO4544  
 Figure 220: DNA304686, NM\_002574, gen.NM\_002574  
 Figure 221: PRO71112  
 Figure 222: DNA323834, NM\_032756, gen.NM\_032756  
 Figure 223: PRO80581  
 Figure 224: DNA323835, XM\_059133, gen.XM\_059133  
 Figure 225: PRO80582  
 Figure 226: DNA323836, XM\_027313, gen.XM\_027313  
 Figure 227: PRO80583  
 Figure 228: DNA323837, XM\_054868, gen.XM\_054868  
 Figure 229: DNA323838, NM\_001262, gen.NM\_001262  
 Figure 230: PRO59546  
 Figure 231: DNA323839, XM\_086391, gen.XM\_086391  
 Figure 232: PRO80584  
 Figure 233: DNA323840, XM\_114798, gen.XM\_114798  
 Figure 234: PRO80585  
 Figure 235: DNA272748, NM\_002979, gen.NM\_002979  
 Figure 236: PRO60860  
 Figure 237: DNA323841, XM\_038911, gen.XM\_038911  
 Figure 238: PRO80586  
 Figure 239: DNA323842, NM\_018070, gen.NM\_018070  
 Figure 240: PRO80587  
 Figure 241: DNA323843, NM\_024603, gen.NM\_024603  
 Figure 242: PRO80588  
 Figure 243: DNA323844, XM\_086389, gen.XM\_086389

Figure 244: DNA323845, XM\_038852,  
gen.XM\_038852  
Figure 245: DNA323846, NM\_032864,  
gen.NM\_032864  
Figure 246: PRO80591  
Figure 247: DNA323847, NM\_024586,  
gen.NM\_024586  
Figure 248: PRO80592  
Figure 249A-B: DNA323848, XM\_097565,  
gen.XM\_097565  
Figure 250: DNA323849, XM\_001472,  
gen.XM\_001472  
Figure 251A-C: DNA323850, XM\_055481,  
gen.XM\_055481  
Figure 252: PRO80593  
Figure 253: DNA323851, XM\_010615,  
gen.XM\_010615  
Figure 254A-B: DNA323852, XM\_089138,  
gen.XM\_089138  
Figure 255: PRO80595  
Figure 256A-B: DNA323853, XM\_059180,  
gen.XM\_059180  
Figure 257: DNA323854, XM\_015717,  
gen.XM\_015717  
Figure 258: PRO80597  
Figure 259: DNA323855, XM\_114125,  
gen.XM\_114125  
Figure 260: DNA323856, NM\_015640,  
gen.NM\_015640  
Figure 261: PRO80599  
Figure 262: DNA323857, NM\_017768,  
gen.NM\_017768  
Figure 263: PRO80600  
Figure 264: DNA323858, XM\_165977,  
gen.XM\_165977  
Figure 265: DNA323859, XM\_086343,  
gen.XM\_086343  
Figure 266: PRO80602  
Figure 267: DNA269708, NM\_007034,  
gen.NM\_007034  
Figure 268: PRO58118  
Figure 269: DNA323860, NM\_001554,  
gen.NM\_001554  
Figure 270: PRO80603  
Figure 271: DNA226260, NM\_006769,  
gen.NM\_006769  
Figure 272: PRO36723  
Figure 273: DNA323861, NM\_004261,  
gen.NM\_004261  
Figure 274: PRO80604  
Figure 275: DNA323862, XM\_165983,  
gen.XM\_165983  
Figure 276: DNA323863, XM\_016164,  
gen.XM\_016164  
Figure 277: DNA323864, XM\_086164,  
gen.XM\_086164

Figure 278: PRO80607  
Figure 279: DNA323865, XM\_086165,  
gen.XM\_086165  
Figure 280: DNA323866, XM\_086167,  
gen.XM\_086167  
Figure 281: DNA323867, XM\_086166,  
gen.XM\_086166  
Figure 282: DNA323868, XM\_086138,  
gen.XM\_086138  
Figure 283: PRO80611  
Figure 284: DNA323869, NM\_000969,  
gen.NM\_000969  
Figure 285: PRO80612  
Figure 286: DNA323870, XM\_088863,  
gen.XM\_088863  
Figure 287: PRO80613  
Figure 288: DNA271003, NM\_003729,  
gen.NM\_003729  
Figure 289: PRO59332  
Figure 290: DNA323871, XM\_165981,  
gen.XM\_165981  
Figure 291: PRO80614  
Figure 292: DNA275139, NM\_013296,  
gen.NM\_013296  
Figure 293: PRO62849  
Figure 294: DNA323872, XM\_058702,  
gen.XM\_058702  
Figure 295: DNA323873, XM\_054978,  
gen.XM\_054978  
Figure 296: DNA323874, NM\_032636,  
gen.NM\_032636  
Figure 297: PRO80617  
Figure 298: DNA323875, NM\_006513,  
gen.NM\_006513  
Figure 299: PRO80618  
Figure 300: DNA323876, NM\_006621,  
gen.NM\_006621  
Figure 301: PRO80619  
Figure 302A-B: DNA323877, NM\_007158,  
gen.NM\_007158  
Figure 303: PRO80620  
Figure 304: DNA323878, XM\_086132,  
gen.XM\_086132  
Figure 305: PRO80621  
Figure 306: DNA323879, NM\_004000,  
gen.NM\_004000  
Figure 307: PRO80622  
Figure 308: DNA323880, NM\_001688,  
gen.NM\_001688  
Figure 309: PRO80623  
Figure 310: DNA323881, NM\_019099,  
gen.NM\_019099  
Figure 311: PRO80624  
Figure 312A-B: DNA323882, NM\_000701,  
gen.NM\_000701  
Figure 313: PRO80625

Figure 314A-B: DNA323883, XM\_018332,  
gen.XM\_018332  
Figure 315A-B: DNA323884, XM\_040709,  
gen.XM\_040709  
Figure 316: PRO80627  
Figure 317: DNA323885, XM\_086518,  
gen.XM\_086518  
Figure 318A-D: DNA323886, XM\_034671,  
gen.XM\_034671  
Figure 319: DNA323887, XM\_034662,  
gen.XM\_034662  
Figure 320: PRO80630  
Figure 321: DNA323888, XM\_039721,  
gen.XM\_039721  
Figure 322: PRO80631  
Figure 323A-B: DNA323889, XM\_086397,  
gen.XM\_086397  
Figure 324A-B: DNA323890, XM\_086515,  
gen.XM\_086515  
Figure 325: PRO80633  
Figure 326: DNA323891, XM\_016480,  
gen.XM\_016480  
Figure 327: DNA323892, XM\_165975,  
gen.XM\_165975  
Figure 328: DNA323893, NM\_016361,  
gen.NM\_016361  
Figure 329: PRO231  
Figure 330: DNA323894, XM\_059210,  
gen.XM\_059210  
Figure 331: DNA323895, XM\_086296,  
gen.XM\_086296  
Figure 332: DNA323896, NM\_030920,  
gen.NM\_030920  
Figure 333: PRO80638  
Figure 334: DNA323897, NM\_016022,  
gen.NM\_016022  
Figure 335: PRO80639  
Figure 336: DNA323898, NM\_031901,  
gen.NM\_031901  
Figure 337: PRO80640  
Figure 338A-B: DNA323899, XM\_088788,  
gen.XM\_088788  
Figure 339: PRO80641  
Figure 340: DNA274759, NM\_005620,  
gen.NM\_005620  
Figure 341: PRO62529  
Figure 342: DNA323900, XM\_001468,  
gen.XM\_001468  
Figure 343: PRO49642  
Figure 344: DNA323901, NM\_006862,  
gen.NM\_006862  
Figure 345: PRO80642  
Figure 346: DNA227529, NM\_002796,  
gen.NM\_002796  
Figure 347: PRO37992  
Figure 348: DNA323902, NM\_002810,

gen.NM\_002810  
Figure 349: PRO61638  
Figure 350: DNA290284, NM\_005997,  
gen.NM\_005997  
Figure 351: PRO70433  
Figure 352: DNA323903, XM\_097639,  
gen.XM\_097639  
Figure 353: DNA323904, XM\_041879,  
gen.XM\_041879  
Figure 354: DNA323905, XM\_041884,  
gen.XM\_041884  
Figure 355: PRO80644  
Figure 356: DNA225809, NM\_000396,  
gen.NM\_000396  
Figure 357: PRO36272  
Figure 358: DNA323906, NM\_025150,  
gen.NM\_025150  
Figure 359: PRO80645  
Figure 360: DNA323907, XM\_114098,  
gen.XM\_114098  
Figure 361: DNA323908, XM\_113369,  
gen.XM\_113369  
Figure 362: PRO80646  
Figure 363: DNA323909, XM\_099467,  
gen.XM\_099467  
Figure 364: DNA323910, NM\_002965,  
gen.NM\_002965  
Figure 365: PRO80648  
Figure 366: DNA323911, XM\_086400,  
gen.XM\_086400  
Figure 367: DNA210134, NM\_014624,  
gen.NM\_014624  
Figure 368: PRO33679  
Figure 369: DNA304666, NM\_002961,  
gen.NM\_002961  
Figure 370: PRO71093  
Figure 371: DNA304720, NM\_019554,  
gen.NM\_019554  
Figure 372: PRO71146  
Figure 373: DNA323912, XM\_165976,  
gen.XM\_165976  
Figure 374: DNA227577, NM\_006271,  
gen.NM\_006271  
Figure 375: PRO38040  
Figure 376: DNA323913, XM\_114097,  
gen.XM\_114097  
Figure 377: DNA323914, XM\_040009,  
gen.XM\_040009  
Figure 378: PRO80651  
Figure 379: DNA323915, NM\_024330,  
gen.NM\_024330  
Figure 380: PRO703  
Figure 381: DNA323916, NM\_012437,  
gen.NM\_012437  
Figure 382: PRO80652  
Figure 383: DNA323917, XM\_086271,

gen.XM.086271  
Figure 384: DNA323918, XM.114055,  
gen.XM.114055  
Figure 385: PRO37535  
Figure 386: DNA323919, XM.113360,  
gen.XM.113360  
Figure 387: PRO80654  
Figure 388: DNA323920, XM.086564,  
gen.XM.086564  
Figure 389: DNA323921, NM.005973,  
gen.NM.005973  
Figure 390: PRO80656  
Figure 391: DNA323922, XM.044077,  
gen.XM.044077  
Figure 392: DNA323923, NM.001878,  
gen.NM.001878  
Figure 393: PRO80657  
Figure 394: DNA323924, NM.021948,  
gen.NM.021948  
Figure 395: PRO6018  
Figure 396: DNA273088, NM.006365,  
gen.NM.006365  
Figure 397: PRO61146  
Figure 398: DNA323925, XM.044127,  
gen.XM.044127  
Figure 399: PRO80658  
Figure 400: DNA323926, XM.053245,  
gen.XM.053245  
Figure 401: PRO80659  
Figure 402: DNA257916, NM.032323,  
gen.NM.032323  
Figure 403: PRO52449  
Figure 404: DNA323927, NM.005572,  
gen.NM.005572  
Figure 405: PRO80660  
Figure 406: DNA323928, XM.044166,  
gen.XM.044166  
Figure 407: PRO80661  
Figure 408: DNA323929, XM.044128,  
gen.XM.044128  
Figure 409: DNA226125, NM.003145,  
gen.NM.003145  
Figure 410: PRO36588  
Figure 411A-B: DNA323930, XM.044172,  
gen.XM.044172  
Figure 412: DNA323931, NM.032292,  
gen.NM.032292  
Figure 413: PRO80664  
Figure 414: DNA323932, NM.004632,  
gen.NM.004632  
Figure 415: PRO80665  
Figure 416: DNA323933, XM.044075,  
gen.XM.044075  
Figure 417: PRO80666  
Figure 418: DNA323934, NM.018253,  
gen.NM.018253

Figure 419: PRO80667  
Figure 420: DNA323935, NM.018116,  
gen.NM.018116  
Figure 421: PRO80668  
Figure 422: DNA323936, NM.002004,  
gen.NM.002004  
Figure 423: PRO80669  
Figure 424: DNA323937, NM.005698,  
gen.NM.005698  
Figure 425: PRO80670  
Figure 426: DNA323938, NM.052837,  
gen.NM.052837  
Figure 427: PRO80671  
Figure 428: DNA194600, NM.006589,  
gen.NM.006589  
Figure 429: PRO23942  
Figure 430: DNA323939, XM.086567,  
gen.XM.086567  
Figure 431: PRO80672  
Figure 432: DNA323940, XM.086552,  
gen.XM.086552  
Figure 433: DNA323941, XM.036744,  
gen.XM.036744  
Figure 434: DNA323942, NM.130898,  
gen.NM.130898  
Figure 435: PRO80675  
Figure 436: DNA226793, NM.006694,  
gen.NM.006694  
Figure 437: PRO37256  
Figure 438: DNA294794, NM.002870,  
gen.NM.002870  
Figure 439: PRO70754  
Figure 440: DNA323943, NM.001030,  
gen.NM.001030  
Figure 441: PRO80676  
Figure 442: DNA323944, XM.036829,  
gen.XM.036829  
Figure 443: PRO80677  
Figure 444: DNA323945, NM.015449,  
gen.NM.015449  
Figure 445: PRO80678  
Figure 446: DNA323946, NM.014847,  
gen.NM.014847  
Figure 447: PRO80679  
Figure 448: DNA323947, XM.036934,  
gen.XM.036934  
Figure 449: PRO80680  
Figure 450A-B: DNA323948, XM.036845,  
gen.XM.036845  
Figure 451: DNA323949, XM.010636,  
gen.XM.010636  
Figure 452: DNA323950, NM.006556,  
gen.NM.006556  
Figure 453: PRO62574  
Figure 454: DNA323951, XM.034082,  
gen.XM.034082

Figure 455: DNA323952, NM\_025207,  
gen.NM\_025207  
Figure 456: PRO80684  
Figure 457: DNA103436, NM\_003815,  
gen.NM\_003815  
Figure 458: PRO4763  
Figure 459: DNA323953, NM\_003516,  
gen.NM\_003516  
Figure 460: PRO80685  
Figure 461: DNA323954, NM\_005850,  
gen.NM\_005850  
Figure 462: PRO59725  
Figure 463A-B: DNA323955, NM\_014849,  
gen.NM\_014849  
Figure 464: PRO80686  
Figure 465: DNA323956, XM\_059094,  
gen.XM\_059094  
Figure 466: DNA323957, XM\_058247,  
gen.XM\_058247  
Figure 467: PRO80688  
Figure 468: DNA323958, NM\_003779,  
gen.NM\_003779  
Figure 469: PRO80689  
Figure 470: DNA323959, NM\_004550,  
gen.NM\_004550  
Figure 471: PRO58974  
Figure 472: DNA323960, XM\_085581,  
gen.XM\_085581  
Figure 473: DNA323961, XM\_113379,  
gen.XM\_113379  
Figure 474: DNA226619, NM\_003564,  
gen.NM\_003564  
Figure 475: PRO37082  
Figure 476A-B: DNA323962, XM\_049680,  
gen.XM\_049680  
Figure 477: DNA323963, XM\_165443,  
gen.XM\_165443  
Figure 478: PRO80693  
Figure 479: DNA323964, XM\_086381,  
gen.XM\_086381  
Figure 480: PRO80694  
Figure 481A-B: DNA323965, NM\_002857,  
gen.NM\_002857  
Figure 482: PRO80695  
Figure 483A-B: DNA323966, XM\_049690,  
gen.XM\_049690  
Figure 484: DNA323967, XM\_114153,  
gen.XM\_114153  
Figure 485: DNA323968, XM\_086378,  
gen.XM\_086378  
Figure 486: DNA323969, XM\_001897,  
gen.XM\_001897  
Figure 487: PRO10002  
Figure 488: DNA323970, NM\_052862,  
gen.NM\_052862  
Figure 489: PRO80699

Figure 490: DNA323971, XM\_086481,  
gen.XM\_086481  
Figure 491: PRO80700  
Figure 492: DNA323972, XM\_059191,  
gen.XM\_059191  
Figure 493: DNA323973, XM\_086485,  
gen.XM\_086485  
Figure 494: DNA323974, XM\_086484,  
gen.XM\_086484  
Figure 495: DNA323975, XM\_047479,  
gen.XM\_047479  
Figure 496: PRO80704  
Figure 497: DNA323976, NM\_003617,  
gen.NM\_003617  
Figure 498: PRO37806  
Figure 499: DNA254298, NM\_025226,  
gen.NM\_025226  
Figure 500: PRO49409  
Figure 501: DNA323977, XM\_034000,  
gen.XM\_034000  
Figure 502: PRO80705  
Figure 503: DNA323978, NM\_032738,  
gen.NM\_032738  
Figure 504: PRO329  
Figure 505: DNA323979, NM\_000569,  
gen.NM\_000569  
Figure 506: PRO80706  
Figure 507: DNA323980, XM\_088945,  
gen.XM\_088945  
Figure 508: PRO80707  
Figure 509: DNA323981, XM\_060331,  
gen.XM\_060331  
Figure 510: PRO80708  
Figure 511: DNA323982, NM\_004905,  
gen.NM\_004905  
Figure 512: PRO80709  
Figure 513: DNA323983, NM\_017847,  
gen.NM\_017847  
Figure 514: PRO80710  
Figure 515A-B: DNA323984, XM\_051877,  
gen.XM\_051877  
Figure 516: PRO62077  
Figure 517: DNA323985, NM\_005717,  
gen.NM\_005717  
Figure 518: PRO80711  
Figure 519A-B: DNA271986, NM\_014837,  
gen.NM\_014837  
Figure 520: PRO60261  
Figure 521A-B: DNA323986, XM\_056923,  
gen.XM\_056923  
Figure 522: DNA323987, XM\_046464,  
gen.XM\_046464  
Figure 523: DNA323988, XM\_002068,  
gen.XM\_002068  
Figure 524A-B: DNA323989, XM\_001289,  
gen.XM\_001289

Figure 525: DNA323990, XM\_114109,  
gen.XM\_114109  
Figure 526: PRO80714  
Figure 527: DNA323991, NM\_022371,  
gen.NM\_022371  
Figure 528: PRO80715  
Figure 529: DNA323992, NM\_004673,  
gen.NM\_004673  
Figure 530: PRO188  
Figure 531: DNA323993, XM\_060517,  
gen.XM\_060517  
Figure 532: DNA323994, XM\_165978,  
gen.XM\_165978  
Figure 533: PRO80717  
Figure 534: DNA323995, XM\_117181,  
gen.XM\_117181  
Figure 535: DNA323996, NM\_018122,  
gen.NM\_018122  
Figure 536: PRO80719  
Figure 537: DNA323997, XM\_042967,  
gen.XM\_042967  
Figure 538: DNA323998, XM\_086494,  
gen.XM\_086494  
Figure 539: PRO80720  
Figure 540: DNA290234, NM\_002923,  
gen.NM\_002923  
Figure 541: PRO70333  
Figure 542: DNA323999, XM\_086328,  
gen.XM\_086328  
Figure 543: DNA324000, XM\_086282,  
gen.XM\_086282  
Figure 544: DNA324001, XM\_053633,  
gen.XM\_053633  
Figure 545: DNA256905, NM\_138391,  
gen.NM\_138391  
Figure 546: PRO51836  
Figure 547: DNA324002, XM\_015434,  
gen.XM\_015434  
Figure 548: DNA324003, NM\_006763,  
gen.NM\_006763  
Figure 549: PRO80725  
Figure 550: DNA227246, NM\_005686,  
gen.NM\_005686  
Figure 551: PRO37709  
Figure 552: DNA324004, XM\_058405,  
gen.XM\_058405  
Figure 553A-B: DNA226005, NM\_000228,  
gen.NM\_000228  
Figure 554: PRO36468  
Figure 555: DNA324005, NM\_015714,  
gen.NM\_015714  
Figure 556: PRO11582  
Figure 557: DNA324006, XM\_086142,  
gen.XM\_086142  
Figure 558: DNA83046, NM\_000574, gen.NM\_000574  
Figure 559: PRO2569

Figure 560A-B: DNA324007, XM\_114030,  
gen.XM\_114030  
Figure 561: DNA324008, XM\_097519,  
gen.XM\_097519  
Figure 562: DNA324009, XM\_059120,  
gen.XM\_059120  
Figure 563: PRO80730  
Figure 564: DNA324010, NM\_016456,  
gen.NM\_016456  
Figure 565: PRO1248  
Figure 566: DNA324011, XM\_036556,  
gen.XM\_036556  
Figure 567: DNA324012, XM\_001914,  
gen.XM\_001914  
Figure 568: DNA324013, XM\_001916,  
gen.XM\_001916  
Figure 569: DNA324014, NM\_018085,  
gen.NM\_018085  
Figure 570: PRO80734  
Figure 571: DNA324015, NM\_006335,  
gen.NM\_006335  
Figure 572: PRO80735  
Figure 573: DNA324016, XM\_036500,  
gen.XM\_036500  
Figure 574: PRO80736  
Figure 575: DNA324017, XM\_036507,  
gen.XM\_036507  
Figure 576: DNA196344, NM\_004767,  
gen.NM\_004767  
Figure 577: PRO24851  
Figure 578: DNA247474, NM\_014176,  
gen.NM\_014176  
Figure 579: PRO44999  
Figure 580A-B: DNA324018, XM\_084055,  
gen.XM\_084055  
Figure 581: DNA324019, XM\_010682,  
gen.XM\_010682  
Figure 582: DNA324020, XM\_117185,  
gen.XM\_117185  
Figure 583: DNA324021, XM\_055880,  
gen.XM\_055880  
Figure 584: PRO80740  
Figure 585: DNA193882, NM\_014184,  
gen.NM\_014184  
Figure 586: PRO23300  
Figure 587: DNA324022, NM\_018212,  
gen.NM\_018212  
Figure 588: PRO80741  
Figure 589: DNA324023, XM\_086431,  
gen.XM\_086431  
Figure 590: PRO80742  
Figure 591: DNA324024, XM\_037329,  
gen.XM\_037329  
Figure 592: DNA324025, XM\_086432,  
gen.XM\_086432  
Figure 593A-B: DNA324026, XM\_010732,



gen.XM\_010732  
Figure 594: DNA227504, NM\_000447,  
gen.NM\_000447  
Figure 595: PRO37967  
Figure 596: DNA324027, NM\_012486,  
gen.NM\_012486  
Figure 597: PRO80745  
Figure 598A-B: DNA324028, XM\_113361,  
gen.XM\_113361  
Figure 599A-B: DNA324029, XM\_001958,  
gen.XM\_001958  
Figure 600: DNA324030, XM\_016199,  
gen.XM\_016199  
Figure 601: DNA324031, XM\_086244,  
gen.XM\_086244  
Figure 602: DNA324032, XM\_086245,  
gen.XM\_086245  
Figure 603: DNA254346, NM\_024709,  
gen.NM\_024709  
Figure 604: PRO49457  
Figure 605: DNA324033, XM\_088107,  
gen.XM\_088107  
Figure 606: DNA324034, NM\_032890,  
gen.NM\_032890  
Figure 607: PRO80752  
Figure 608: DNA324035, XM\_052974,  
gen.XM\_052974  
Figure 609: PRO80753  
Figure 610: DNA324036, XM\_047499,  
gen.XM\_047499  
Figure 611: PRO80754  
Figure 612: DNA324037, NM\_000858,  
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Figure 613: PRO80755  
Figure 614: DNA324038, NM\_024319,  
gen.NM\_024319  
Figure 615: PRO80756  
Figure 616: DNA324039, XM\_047545,  
gen.XM\_047545  
Figure 617: PRO4914  
Figure 618A-B: DNA324040, XM\_056884,  
gen.XM\_056884  
Figure 619: DNA324041, XM\_098599,  
gen.XM\_098599  
Figure 620: DNA324042, XM\_165439,  
gen.XM\_165439  
Figure 621: PRO80759  
Figure 622: DNA324043, XM\_089030,  
gen.XM\_089030  
Figure 623: PRO80760  
Figure 624: DNA82328, NM\_000029, gen.NM\_000029  
Figure 625: PRO1707  
Figure 626: DNA324044, NM\_014236,  
gen.NM\_014236  
Figure 627: PRO80761  
Figure 628: DNA324045, XM\_056970,

gen.XM\_056970  
Figure 629: PRO80762  
Figure 630: DNA324046, NM\_032324,  
gen.NM\_032324  
Figure 631: PRO80763  
Figure 632: DNA324047, XM\_086257,  
gen.XM\_086257  
Figure 633: PRO80764  
Figure 634: DNA324048, XM\_114137,  
gen.XM\_114137  
Figure 635: PRO80765  
Figure 636: DNA324049, NM\_000143,  
gen.NM\_000143  
Figure 637: PRO62607  
Figure 638: DNA324050, XM\_090833,  
gen.XM\_090833  
Figure 639: DNA324051, NM\_130398,  
gen.NM\_130398  
Figure 640: PRO80767  
Figure 641: DNA324052, XM\_117196,  
gen.XM\_117196  
Figure 642: DNA324053, XM\_018041,  
gen.XM\_018041  
Figure 643: DNA324054, NM\_001011,  
gen.NM\_001011  
Figure 644: PRO10692  
Figure 645: DNA324055, NM\_024027,  
gen.NM\_024027  
Figure 646: PRO1182  
Figure 647: DNA324056, NM\_016030,  
gen.NM\_016030  
Figure 648: PRO80770  
Figure 649: DNA103217, NM\_003310,  
gen.NM\_003310  
Figure 650: PRO4547  
Figure 651: DNA275195, NM\_001034,  
gen.NM\_001034  
Figure 652: PRO62893  
Figure 653: DNA324057, XM\_059368,  
gen.XM\_059368  
Figure 654: PRO80771  
Figure 655: DNA324058, NM\_006826,  
gen.NM\_006826  
Figure 656: PRO70258  
Figure 657: DNA324059, NM\_005378,  
gen.NM\_005378  
Figure 658: PRO80772  
Figure 659: DNA324060, NM\_002539,  
gen.NM\_002539  
Figure 660: PRO80773  
Figure 661: DNA324061, XM\_096149,  
gen.XM\_096149  
Figure 662: DNA275049, NM\_004939,  
gen.NM\_004939  
Figure 663: PRO62770  
Figure 664A-B: DNA324062, XM\_036450,

gen.XM\_036450  
Figure 665: DNA324063, XM\_103946,  
gen.XM\_103946  
Figure 666: PRO80775  
Figure 667: DNA324064, NM\_014713,  
gen.NM\_014713  
Figure 668: PRO80776  
Figure 669: DNA324065, XM\_087206,  
gen.XM\_087206  
Figure 670: DNA324066, NM\_106552,  
gen.NM\_106552  
Figure 671: PRO80778  
Figure 672: DNA324067, XM\_092135,  
gen.XM\_092135  
Figure 673: PRO80779  
Figure 674: DNA324068, NM\_017910,  
gen.NM\_017910  
Figure 675: PRO80780  
Figure 676: DNA324069, XM\_092517,  
gen.XM\_092517  
Figure 677: PRO80781  
Figure 678A-B: DNA324070, NM\_025203,  
gen.NM\_025203  
Figure 679: PRO80782  
Figure 680: DNA324071, XM\_002480,  
gen.XM\_002480  
Figure 681: DNA324072, NM\_002707,  
gen.NM\_002707  
Figure 682: PRO12199  
Figure 683: DNA324073, XM\_087151,  
gen.XM\_087151  
Figure 684: DNA227165, NM\_014748,  
gen.NM\_014748  
Figure 685: PRO37628  
Figure 686: DNA324074, NM\_015636,  
gen.NM\_015636  
Figure 687: PRO80785  
Figure 688: DNA273800, NM\_001521,  
gen.NM\_001521  
Figure 689: PRO61761  
Figure 690: DNA324075, XM\_047175,  
gen.XM\_047175  
Figure 691: PRO80786  
Figure 692A-B: DNA324076, NM\_004341,  
gen.NM\_004341  
Figure 693: PRO80787  
Figure 694: DNA324077, NM\_016085,  
gen.NM\_016085  
Figure 695: PRO80788  
Figure 696: DNA324078, NM\_080592,  
gen.NM\_080592  
Figure 697: PRO80789  
Figure 698: DNA227545, NM\_021095,  
gen.NM\_021095  
Figure 699: PRO38008  
Figure 700: DNA324079, XM\_002435,

gen.XM\_002435  
Figure 701: DNA324080, NM\_000221,  
gen.NM\_000221  
Figure 702: PRO80790  
Figure 703: DNA271243, NM\_006488,  
gen.NM\_006488  
Figure 704: PRO59558  
Figure 705: DNA324081, NM\_007046,  
gen.NM\_007046  
Figure 706: PRO9886  
Figure 707: DNA324082, NM\_021831,  
gen.NM\_021831  
Figure 708: PRO80791  
Figure 709: DNA324083, NM\_020134,  
gen.NM\_020134  
Figure 710: PRO80792  
Figure 711: DNA103593, NM\_000183,  
gen.NM\_000183  
Figure 712: PRO4917  
Figure 713: DNA324084, NM\_000182,  
gen.NM\_000182  
Figure 714: PRO80793  
Figure 715: DNA324085, XM\_097976,  
gen.XM\_097976  
Figure 716A-B: DNA324086, XM\_039712,  
gen.XM\_039712  
Figure 717: DNA324087, NM\_022552,  
gen.NM\_022552  
Figure 718: PRO80796  
Figure 719: DNA324088, NM\_024572,  
gen.NM\_024572  
Figure 720: PRO80797  
Figure 721: DNA324089, NM\_018607,  
gen.NM\_018607  
Figure 722: PRO80798  
Figure 723: DNA324090, XM\_165448,  
gen.XM\_165448  
Figure 724: PRO80799  
Figure 725: DNA324091, XM\_087195,  
gen.XM\_087195  
Figure 726: DNA324092, XM\_087193,  
gen.XM\_087193  
Figure 727: DNA324093, NM\_138801,  
gen.NM\_138801  
Figure 728: PRO80802  
Figure 729: DNA324094, XM\_098004,  
gen.XM\_098004  
Figure 730: PRO80803  
Figure 731: DNA324095, XM\_031519,  
gen.XM\_031519  
Figure 732: PRO80804  
Figure 733A-B: DNA324096, XM\_031527,  
gen.XM\_031527  
Figure 734: DNA324097, XM\_038576,  
gen.XM\_038576  
Figure 735: PRO80806

Figure 736: DNA324098, XM\_117264,  
gen.XM\_117264  
Figure 737: PRO80807  
Figure 738A-B: DNA324099, XM\_031626,  
gen.XM\_031626  
Figure 739: PRO80808  
Figure 740: DNA324100, XM\_057664,  
gen.XM\_057664  
Figure 741: DNA226428, NM\_000251,  
gen.NM\_000251  
Figure 742: PRO36891  
Figure 743: DNA324101, XM\_087211,  
gen.XM\_087211  
Figure 744A-B: DNA275066, NM\_000179,  
gen.NM\_000179  
Figure 745: PRO62786  
Figure 746A-C: DNA270154, NM\_003128,  
gen.NM\_003128  
Figure 747: PRO58543  
Figure 748: DNA324102, XM\_087051,  
gen.XM\_087051  
Figure 749: DNA324103, NM\_002954,  
gen.NM\_002954  
Figure 750: PRO62239  
Figure 751: DNA271060, NM\_002453,  
gen.NM\_002453  
Figure 752: PRO59384  
Figure 753: DNA324104, XM\_048088,  
gen.XM\_048088  
Figure 754: PRO80811  
Figure 755: DNA324105, XM\_010886,  
gen.XM\_010886  
Figure 756: PRO80812  
Figure 757: DNA324106, XM\_045283,  
gen.XM\_045283  
Figure 758: PRO80813  
Figure 759: DNA324107, NM\_006430,  
gen.NM\_006430  
Figure 760: PRO80814  
Figure 761A-B: DNA324108, NM\_003400,  
gen.NM\_003400  
Figure 762: PRO59544  
Figure 763: DNA324109, XM\_018301,  
gen.XM\_018301  
Figure 764: DNA324110, NM\_005917,  
gen.NM\_005917  
Figure 765: PRO4918  
Figure 766: DNA324111, XM\_016843,  
gen.XM\_016843  
Figure 767: PRO80816  
Figure 768: DNA324112, XM\_088638,  
gen.XM\_088638  
Figure 769: PRO80817  
Figure 770: DNA324113, XM\_002647,  
gen.XM\_002647  
Figure 771: DNA324114, XM\_010881,

gen.XM\_010881  
Figure 772: DNA324115, XM\_087069,  
gen.XM\_087069  
Figure 773: DNA324116, XM\_016625,  
gen.XM\_016625  
Figure 774: PRO80820  
Figure 775: DNA324117, XM\_087068,  
gen.XM\_087068  
Figure 776: DNA324118, XM\_002674,  
gen.XM\_002674  
Figure 777: DNA324119, XM\_065884,  
gen.XM\_065884  
Figure 778: PRO80823  
Figure 779A-B: DNA324120, XM\_002739,  
gen.XM\_002739  
Figure 780: DNA324121, XM\_031596,  
gen.XM\_031596  
Figure 781: PRO61325  
Figure 782: DNA324122, XM\_031585,  
gen.XM\_031585  
Figure 783: DNA324123, XM\_031586,  
gen.XM\_031586  
Figure 784: DNA324124, XM\_018039,  
gen.XM\_018039  
Figure 785: DNA324125, NM\_032822,  
gen.NM\_032822  
Figure 786: PRO80827  
Figure 787A-B: DNA324126, XM\_096172,  
gen.XM\_096172  
Figure 788A-B: DNA324127, XM\_002727,  
gen.XM\_002727  
Figure 789: DNA324128, NM\_003124,  
gen.NM\_003124  
Figure 790: PRO80830  
Figure 791: DNA324129, XM\_086980,  
gen.XM\_086980  
Figure 792: DNA227795, NM\_006429,  
gen.NM\_006429  
Figure 793: PRO38258  
Figure 794: DNA287167, NM\_006636,  
gen.NM\_006636  
Figure 795: PRO59136  
Figure 796: DNA324130, NM\_033046,  
gen.NM\_033046  
Figure 797: PRO80832  
Figure 798: DNA324131, NM\_133637,  
gen.NM\_133637  
Figure 799: PRO80833  
Figure 800: DNA324132, XM\_035220,  
gen.XM\_035220  
Figure 801: DNA324133, NM\_013247,  
gen.NM\_013247  
Figure 802: PRO80835  
Figure 803: DNA227528, NM\_021103,  
gen.NM\_021103  
Figure 804: PRO37991

Figure 805: DNA324134, XM\_086920,  
gen.XM\_086920  
Figure 806: DNA150725, NM\_001747,  
gen.NM\_001747  
Figure 807: PRO12792  
Figure 808: DNA324135, NM\_005911,  
gen.NM\_005911  
Figure 809: PRO80837  
Figure 810: DNA324136, NM\_032827,  
gen.NM\_032827  
Figure 811: PRO80838  
Figure 812: DNA324137, NM\_017952,  
gen.NM\_017952  
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gen.NM\_006839  
Figure 815: PRO37653  
Figure 816: DNA324138, XM\_114215,  
gen.XM\_114215  
Figure 817: DNA324139, XM\_052989,  
gen.XM\_052989  
Figure 818: DNA324140, XM\_049116,  
gen.XM\_049116  
Figure 819: PRO80842  
Figure 820A-B: DNA324141, XM\_049108,  
gen.XM\_049108  
Figure 821: PRO80843  
Figure 822: DNA324142, XM\_049113,  
gen.XM\_049113  
Figure 823: DNA324143, XM\_002611,  
gen.XM\_002611  
Figure 824A-B: DNA324144, XM\_114247,  
gen.XM\_114247  
Figure 825: DNA324145, NM\_017789,  
gen.NM\_017789  
Figure 826: PRO80846  
Figure 827: DNA324146, NM\_001862,  
gen.NM\_001862  
Figure 828: PRO80847  
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gen.NM\_005783  
Figure 830: PRO80848  
Figure 831A-B: DNA324148, XM\_037108,  
gen.XM\_037108  
Figure 832: DNA324149, NM\_000993,  
gen.NM\_000993  
Figure 833: PRO11197  
Figure 834: DNA324150, NM\_017546,  
gen.NM\_017546  
Figure 835: PRO80850  
Figure 836: DNA324151, NM\_001450,  
gen.NM\_001450  
Figure 837: PRO80851  
Figure 838: DNA324152, XM\_114229,  
gen.XM\_114229  
Figure 839: DNA324153, XM\_087122,

gen.XM\_087122  
Figure 840: PRO80853  
Figure 841: DNA324154, XM\_018540,  
gen.XM\_018540  
Figure 842: DNA324155, XM\_087040,  
gen.XM\_087040  
Figure 843: DNA324156, NM\_032212,  
gen.NM\_032212  
Figure 844: PRO80856  
Figure 845: DNA324157, XM\_002217,  
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Figure 846: PRO80857  
Figure 847: DNA324158, NM\_000576,  
gen.NM\_000576  
Figure 848: PRO65  
Figure 849: DNA324159, XM\_086923,  
gen.XM\_086923  
Figure 850: DNA324160, XM\_086925,  
gen.XM\_086925  
Figure 851A-B: DNA324161, XM\_114266,  
gen.XM\_114266  
Figure 852: PRO80860  
Figure 853: DNA324162, XM\_002704,  
gen.XM\_002704  
Figure 854: DNA194740, NM\_005291,  
gen.NM\_005291  
Figure 855: PRO24028  
Figure 856A-B: DNA324163, XM\_114267,  
gen.XM\_114267  
Figure 857: DNA324164, XM\_034952,  
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Figure 858: DNA324165, XM\_086950,  
gen.XM\_086950  
Figure 859A-B: DNA255531, NM\_017751,  
gen.NM\_017751  
Figure 860: PRO50596  
Figure 861: DNA324166, XM\_017698,  
gen.XM\_017698  
Figure 862: DNA324167, XM\_030529,  
gen.XM\_030529  
Figure 863: PRO80866  
Figure 864: DNA275240, NM\_005915,  
gen.NM\_005915  
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Figure 866: DNA324168, XM\_043173,  
gen.XM\_043173  
Figure 867: DNA324169, XM\_092489,  
gen.XM\_092489  
Figure 868: PRO80868  
Figure 869: DNA324170, XM\_115672,  
gen.XM\_115672  
Figure 870: PRO80869  
Figure 871: DNA324171, NM\_020548,  
gen.NM\_020548  
Figure 872: PRO60753  
Figure 873: DNA324172, XM\_037101,

gen.XM\_037101  
Figure 874: PRO80870  
Figure 875: DNA324173, NM\_032390, gen.NM\_032390  
Figure 876: PRO80871  
Figure 877: DNA324174, XM\_002447, gen.XM\_002447  
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Figure 879: PRO80873  
Figure 880: DNA324176, XM\_016288, gen.XM\_016288  
Figure 881: DNA272127, NM\_003937, gen.NM\_003937  
Figure 882: PRO60397  
Figure 883: DNA324177, XM\_030582, gen.XM\_030582  
Figure 884: PRO80875  
Figure 885: DNA324178, NM\_015702, gen.NM\_015702  
Figure 886: PRO80876  
Figure 887: DNA324179, NM\_016838, gen.NM\_016838  
Figure 888: PRO80877  
Figure 889: DNA324180, NM\_016839, gen.NM\_016839  
Figure 890: PRO80878  
Figure 891: DNA324181, XM\_087118, gen.XM\_087118  
Figure 892: PRO80879  
Figure 893: DNA324182, XM\_165998, gen.XM\_165998  
Figure 894: DNA324183, NM\_001935, gen.NM\_001935  
Figure 895: PRO80881  
Figure 896: DNA324184, NM\_020675, gen.NM\_020675  
Figure 897: PRO80882  
Figure 898: DNA88051, NM\_000079, gen.NM\_000079  
Figure 899: PRO2146  
Figure 900: DNA324185, XM\_166008, gen.XM\_166008  
Figure 901: DNA324186, XM\_087240, gen.XM\_087240  
Figure 902: PRO11403  
Figure 903: DNA324187, NM\_013341, gen.NM\_013341  
Figure 904: PRO80883  
Figure 905: DNA304805, NM\_031942, gen.NM\_031942  
Figure 906: PRO69531  
Figure 907: DNA324188, XM\_059465, gen.XM\_059465  
Figure 908: PRO80884  
Figure 909: DNA324189, XM\_015920, gen.XM\_015920  
Figure 910: DNA324190, XM\_166007, gen.XM\_166007  
Figure 911: DNA324191, XM\_015922, gen.XM\_015922  
Figure 912: DNA324192, XM\_087061, gen.XM\_087061  
Figure 913: PRO80888  
Figure 914: DNA324193, XM\_087062, gen.XM\_087062  
Figure 915: PRO80889  
Figure 916: DNA324194, NM\_001463, gen.NM\_001463  
Figure 917: PRO80890  
Figure 918: DNA324195, XM\_092158, gen.XM\_092158  
Figure 919: PRO80891  
Figure 920: DNA324196, XM\_059351, gen.XM\_059351  
Figure 921A-B: DNA324197, NM\_000090, gen.NM\_000090  
Figure 922: PRO2665  
Figure 923: DNA324198, NM\_014585, gen.NM\_014585  
Figure 924: PRO37675  
Figure 925: DNA324199, XM\_010778, gen.XM\_010778  
Figure 926: DNA324200, XM\_086961, gen.XM\_086961  
Figure 927: DNA324201, XM\_165994, gen.XM\_165994  
Figure 928: DNA324202, XM\_045170, gen.XM\_045170  
Figure 929: DNA324203, XM\_113390, gen.XM\_113390  
Figure 930: DNA299899, NM\_002157, gen.NM\_002157  
Figure 931: PRO62760  
Figure 932: DNA324204, XM\_087045, gen.XM\_087045  
Figure 933: DNA324205, XM\_086944, gen.XM\_086944  
Figure 934: DNA271608, NM\_014670, gen.NM\_014670  
Figure 935: PRO59895  
Figure 936: DNA324206, XM\_027963, gen.XM\_027963  
Figure 937: PRO80900  
Figure 938: DNA324207, XM\_010852, gen.XM\_010852  
Figure 939: PRO80901  
Figure 940: DNA324208, XM\_028034, gen.XM\_028034  
Figure 941: DNA324209, NM\_015934, gen.NM\_015934  
Figure 942: DNA324210, XM\_087028, gen.XM\_087028

Figure 943: PRO80903  
Figure 944: DNA324211, XM\_092346,  
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Figure 945: PRO80904  
Figure 946: DNA324212, XM\_002669,  
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Figure 947: PRO80905  
Figure 948: DNA324213, NM\_021121,  
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Figure 949: PRO23124  
Figure 950: DNA324214, NM\_001959,  
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Figure 951: PRO23124  
Figure 952: DNA324215, XM\_030834,  
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Figure 953: PRO80906  
Figure 954A-C: DNA324216, XM\_055254,  
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Figure 955: DNA324217, NM\_004044,  
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Figure 956: PRO80908  
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Figure 958: DNA324219, NM\_021141,  
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Figure 959: PRO59313  
Figure 960A-B: DNA324220, XM\_098048,  
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Figure 961: PRO80910  
Figure 962: DNA324221, XM\_098047,  
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Figure 963: PRO80911  
Figure 964: DNA324222, XM\_002636,  
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Figure 965: DNA324223, XM\_087181,  
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Figure 966: DNA324224, NM\_000998,  
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Figure 967: PRO10498  
Figure 968: DNA324225, XM\_059422,  
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Figure 969: PRO9984  
Figure 970: DNA324226, XM\_092545,  
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Figure 971: DNA324227, XM\_059461,  
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Figure 972: PRO80915  
Figure 973: DNA324228, NM\_018674,  
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Figure 974: PRO80916  
Figure 975: DNA324229, XM\_050962,  
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Figure 976: PRO80917  
Figure 977: DNA194827, NM\_012100,  
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Figure 978: PRO24091

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Figure 980A-B: DNA324231, NM\_002846,  
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Figure 982: DNA324232, NM\_006000,  
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Figure 983: PRO26228  
Figure 984: DNA324233, XM\_050891,  
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Figure 985: DNA324234, XM\_087162,  
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Figure 986: DNA324235, XM\_058098,  
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Figure 988: DNA324236, NM\_022453,  
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Figure 989: PRO80921  
Figure 990: DNA324237, NM\_032726,  
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Figure 991: PRO70675  
Figure 992: DNA324238, XM\_010866,  
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Figure 993: DNA324239, XM\_087166,  
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Figure 994: DNA254204, NM\_001087,  
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Figure 995: PRO49316  
Figure 996: DNA324240, NM\_005731,  
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Figure 997: PRO80924  
Figure 998: DNA189697, NM\_004846,  
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Figure 999: PRO23123  
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Figure 1002: DNA324242, XM\_115825,  
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Figure 1003: PRO80926  
Figure 1004: DNA324243, XM\_010858,  
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Figure 1005: PRO80927  
Figure 1006: DNA324244, XM\_002540,  
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Figure 1007: DNA324245, XM\_048690,  
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Figure 1008: PRO80929  
Figure 1009: DNA324246, NM\_030926,  
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Figure 1010: PRO80930  
Figure 1011: DNA324247, XM\_087218,  
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Figure 1012: DNA324248, NM\_004509,  
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Figure 1013: PRO80932

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Figure 1015: PRO80933  
Figure 1016: DNA324250, NM\_080424,  
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Figure 1017: PRO80934  
Figure 1018: DNA324251, NM\_018410,  
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Figure 1019: PRO80935  
Figure 1020: DNA324252, NM\_017974,  
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Figure 1021: PRO80936  
Figure 1022A-B: DNA324253, XM\_096169,  
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Figure 1023: PRO80937  
Figure 1024: DNA150884, NM\_005855,  
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Figure 1025: PRO12520  
Figure 1026A-B: DNA324254, NM\_004735,  
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Figure 1027: PRO80938  
Figure 1028A-C: DNA324255, XM\_030203,  
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Figure 1029: DNA324256, XM\_059372,  
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Figure 1030: DNA324257, NM\_002712,  
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Figure 1032A-B: DNA324258, XM\_042326,  
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Figure 1033: PRO80942  
Figure 1034: DNA324259, NM\_004404,  
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Figure 1035: PRO80943  
Figure 1036: DNA324260, XM\_002742,  
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Figure 1037: DNA324261, NM\_138483,  
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Figure 1038: PRO80945  
Figure 1039: DNA324262, XM\_115706,  
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Figure 1040: DNA324263, XM\_115722,  
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Figure 1041: DNA324264, XM\_084141,  
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Figure 1042: DNA324265, XM\_005086,  
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Figure 1043: DNA324266, NM\_015453,  
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Figure 1044: PRO80949  
Figure 1045: DNA324267, NM\_022485,  
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Figure 1046: PRO80950  
Figure 1047A-B: DNA324268, XM\_054520,  
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Figure 1048: PRO80951

Figure 1049: DNA324269, NM\_006354,  
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Figure 1050: PRO80952  
Figure 1051: DNA324270, NM\_133480,  
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Figure 1052: PRO80953  
Figure 1053: DNA324271, NM\_133481,  
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Figure 1054: PRO80954  
Figure 1055: DNA324272, NM\_005718,  
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Figure 1056: PRO80955  
Figure 1057: DNA324273, NM\_015644,  
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Figure 1058: PRO80956  
Figure 1059: DNA324274, XM\_059561,  
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Figure 1060: DNA324275, XM\_052310,  
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Figure 1061: PRO80958  
Figure 1062: DNA269910, NM\_006395,  
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Figure 1063: PRO58308  
Figure 1064: DNA324276, NM\_000994,  
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Figure 1065: PRO80959  
Figure 1066: DNA151017, NM\_004844,  
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Figure 1067: PRO12841  
Figure 1068: DNA324277, XM\_059557,  
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Figure 1069: PRO80960  
Figure 1070A-B: DNA324278, XM\_042860,  
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Figure 1071: PRO80961  
Figure 1072: DNA324279, XM\_042841,  
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Figure 1073: PRO80962  
Figure 1074: DNA324280, XM\_053712,  
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Figure 1075: DNA324281, XM\_087284,  
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Figure 1076: DNA324282, NM\_002948,  
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Figure 1077: PRO6360  
Figure 1078: DNA324283, XM\_053323,  
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Figure 1079A-B: DNA324284, NM\_001068,  
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Figure 1080: PRO80966  
Figure 1081: DNA252367, NM\_017801,  
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Figure 1082: PRO48357  
Figure 1083: DNA324285, XM\_093624,  
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Figure 1084: PRO80967

Figure 1085: DNA324286, XM\_046401,  
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Figure 1086: DNA324287, NM\_022461,  
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Figure 1087: PRO80969  
Figure 1088: DNA324288, XM\_113410,  
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Figure 1089: DNA88100, NM\_000404,  
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Figure 1090: PRO2172  
Figure 1091: DNA324289, XM\_091076,  
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Figure 1092: PRO80970  
Figure 1093A-B: DNA271187, NM\_005109,  
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Figure 1094: PRO59504  
Figure 1095: DNA324290, NM\_002468,  
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Figure 1096: PRO36735  
Figure 1097: DNA269930, NM\_001607,  
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Figure 1098: PRO58328  
Figure 1099: DNA270401, NM\_003149,  
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Figure 1101: DNA324291, XM\_087370,  
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Figure 1102: PRO80971  
Figure 1103: DNA324292, XM\_098158,  
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Figure 1104: PRO80972  
Figure 1105: DNA324293, XM\_017364,  
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Figure 1106: DNA324294, XM\_087349,  
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Figure 1107: PRO80974  
Figure 1108: DNA226547, NM\_002295,  
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Figure 1109: PRO37010  
Figure 1110: DNA324295, NM\_003973,  
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Figure 1111: PRO80975  
Figure 1112: DNA324296, XM\_030417,  
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Figure 1113: DNA324297, NM\_020347,  
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Figure 1114: PRO80977  
Figure 1115: DNA324298, XM\_087346,  
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Figure 1116: PRO80978  
Figure 1117: DNA324299, XM\_096198,  
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Figure 1118: PRO80979  
Figure 1119: DNA324300, XM\_003222,  
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Figure 1120: DNA324301, XM\_087588,

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Figure 1121: DNA324302, XM\_166011,  
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Figure 1122A-B: DNA324303, XM\_114364,  
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Figure 1123A-B: DNA324304, XM\_033294,  
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Figure 1124: PRO80983  
Figure 1125: DNA324305, NM\_138614,  
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Figure 1126: PRO80984  
Figure 1127: DNA324306, XM\_002899,  
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Figure 1128: DNA225910, NM\_004345,  
gen.NM\_004345  
Figure 1129: PRO36373  
Figure 1130: DNA324307, XM\_010953,  
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Figure 1131: DNA324308, XM\_051518,  
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Figure 1132A-D: DNA324309, NM\_001407,  
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Figure 1133: PRO50095  
Figure 1134: DNA324310, NM\_003365,  
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Figure 1135: PRO80988  
Figure 1136: DNA324311, XM\_003245,  
gen.XM\_003245  
Figure 1137: DNA324312, XM\_047561,  
gen.XM\_047561  
Figure 1138: PRO80990  
Figure 1139: DNA324313, XM\_116853,  
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Figure 1140A-B: DNA324314, XM\_113405,  
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Figure 1141: DNA324315, XM\_114323,  
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Figure 1142: PRO80993  
Figure 1143: DNA324316, XM\_002828,  
gen.XM\_002828  
Figure 1144: PRO80994  
Figure 1145: DNA150976, NM\_022171,  
gen.NM\_022171  
Figure 1146: PRO12565  
Figure 1147: DNA324317, XM\_041507,  
gen.XM\_041507  
Figure 1148: PRO71103  
Figure 1149: DNA103505, NM\_004636,  
gen.NM\_004636  
Figure 1150: PRO4832  
Figure 1151: DNA324318, NM\_006764,  
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Figure 1152: PRO80995  
Figure 1153: DNA150562, NM\_007275,  
gen.NM\_007275  
Figure 1154: PRO12779



Figure 1155: DNA254582, NM\_004635,  
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Figure 1156: PRO49685  
Figure 1157: DNA324319, NM\_052859,  
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Figure 1158: PRO80996  
Figure 1159: DNA324320, NM\_001064,  
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Figure 1160: PRO80997  
Figure 1161: DNA324321, XM\_041211,  
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Figure 1162: DNA324322, XM\_003213,  
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Figure 1163A-C: DNA324323, XM\_037423,  
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Figure 1164: PRO80999  
Figure 1165A-B: DNA227307, NM\_007184,  
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Figure 1166: PRO37770  
Figure 1167: DNA324324, NM\_000688,  
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Figure 1168: PRO81000  
Figure 1169: DNA324325, XM\_067715,  
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Figure 1170: DNA324326, NM\_000992,  
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Figure 1171: PRO62153  
Figure 1172: DNA324327, NM\_000666,  
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Figure 1173: PRO81002  
Figure 1174: DNA324328, NM\_032750,  
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Figure 1175: PRO81003  
Figure 1176: DNA324329, NM\_033008,  
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Figure 1177: PRO81004  
Figure 1178: DNA324330, NM\_033010,  
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Figure 1179: PRO81005  
Figure 1180: DNA324331, NM\_020418,  
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Figure 1181: PRO81006  
Figure 1182: DNA273919, NM\_004704,  
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Figure 1183: PRO61870  
Figure 1184A-B: DNA324332, XM\_087448,  
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Figure 1185: PRO81007  
Figure 1186: DNA324333, XM\_002855,  
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Figure 1187: DNA324334, XM\_002854,  
gen.XM\_002854  
Figure 1188: DNA0, NM\_002854, gen.NM\_002854  
Figure 1189: PRO  
Figure 1190: DNA324335, XM\_096195,  
gen.XM\_096195

Figure 1191: PRO81010  
Figure 1192: DNA324336, XM\_166015,  
gen.XM\_166015  
Figure 1193: DNA324337, XM\_113395,  
gen.XM\_113395  
Figure 1194: PRO81012  
Figure 1195: DNA269730, NM\_014814,  
gen.NM\_014814  
Figure 1196: PRO58140  
Figure 1197: DNA324338, XM\_036938,  
gen.XM\_036938  
Figure 1198: DNA324339, XM\_029369,  
gen.XM\_029369  
Figure 1199: DNA324340, XM\_076414,  
gen.XM\_076414  
Figure 1200: PRO81015  
Figure 1201: DNA324341, XM\_093546,  
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Figure 1202: DNA324342, XM\_113409,  
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Figure 1203: DNA324343, XM\_087268,  
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Figure 1204: DNA324344, XM\_116071,  
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Figure 1205: DNA324345, XM\_116072,  
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Figure 1206: DNA324346, NM\_000986,  
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Figure 1207: PRO10602  
Figure 1208: DNA324347, XM\_015462,  
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Figure 1209: DNA324348, XM\_167366,  
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Figure 1210: PRO81022  
Figure 1211: DNA324349, XM\_087331,  
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Figure 1212: PRO81023  
Figure 1213: DNA324350, XM\_039952,  
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Figure 1214: DNA324351, XM\_045290,  
gen.XM\_045290  
Figure 1215: PRO81025  
Figure 1216A-B: DNA324352, NM\_007085,  
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Figure 1217: PRO2077  
Figure 1218: DNA324353, NM\_004547,  
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Figure 1219: PRO81026  
Figure 1220: DNA324354, XM\_027161,  
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Figure 1221A-B: DNA324355, XM\_032269,  
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Figure 1222: PRO81028  
Figure 1223: DNA88547, NM\_006810,  
gen.NM\_006810  
Figure 1224: PRO2837

Figure 1225: DNA324356, XM\_114301,  
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Figure 1226: PRO81029  
Figure 1227: DNA324357, XM\_098173,  
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Figure 1228: PRO81030  
Figure 1229: DNA324358, XM\_042618,  
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Figure 1230: PRO81031  
Figure 1231: DNA324359, XM\_084129,  
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Figure 1232: DNA324360, XM\_098154,  
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Figure 1233: PRO81033  
Figure 1234: DNA324361, XM\_050552,  
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Figure 1235: DNA324362, NM\_032343,  
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Figure 1236: PRO81034  
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Figure 1238A-B: DNA324364, NM\_013336,  
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Figure 1239: PRO1314  
Figure 1240: DNA324365, XM\_067264,  
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Figure 1241: PRO81036  
Figure 1242: DNA324366, XM\_114309,  
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Figure 1243: DNA324367, XM\_084111,  
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Figure 1244: DNA324368, XM\_113397,  
gen.XM\_113397  
Figure 1245: DNA324369, XM\_098111,  
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Figure 1246: DNA324370, NM\_004637,  
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Figure 1247: PRO81040  
Figure 1248: DNA324371, NM\_020701,  
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Figure 1249: PRO81041  
Figure 1250: DNA324372, NM\_003418,  
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Figure 1251: PRO81042  
Figure 1252: DNA324373, XM\_059583,  
gen.XM\_059583  
Figure 1253: PRO81043  
Figure 1254: DNA324374, XM\_113417,  
gen.XM\_113417  
Figure 1255: DNA324375, XM\_093487,  
gen.XM\_093487  
Figure 1256A-B: DNA324376, XM\_030812,  
gen.XM\_030812  
Figure 1257: PRO58177  
Figure 1258A-B: DNA324377, XM\_039805,  
gen.XM\_039805

Figure 1259: PRO81046  
Figure 1260: DNA324378, NM\_000532,  
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Figure 1261: PRO81047  
Figure 1262: DNA324379, XM\_036118,  
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Figure 1263: DNA324380, XM\_084123,  
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Figure 1264: DNA324381, XM\_018149,  
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Figure 1265: DNA324382, XM\_087342,  
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Figure 1266: DNA324383, XM\_059516,  
gen.XM\_059516  
Figure 1267: DNA324384, XM\_087341,  
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Figure 1268: DNA324385, XM\_165451,  
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Figure 1269: PRO81053  
Figure 1270: DNA269858, NM\_004766,  
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Figure 1271: PRO58259  
Figure 1272: DNA324386, NM\_030921,  
gen.NM\_030921  
Figure 1273: PRO51109  
Figure 1274: DNA324387, XM\_002859,  
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Figure 1275: DNA324388, XM\_166014,  
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Figure 1276: DNA324389, NM\_013363,  
gen.NM\_013363  
Figure 1277: PRO287  
Figure 1278: DNA324390, XM\_058267,  
gen.XM\_058267  
Figure 1279: PRO81056  
Figure 1280A-B: DNA324391, NM\_032383,  
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Figure 1281: PRO81057  
Figure 1282: DNA324392, NM\_015472,  
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Figure 1283: PRO81058  
Figure 1284: DNA324393, NM\_014445,  
gen.NM\_014445  
Figure 1285: PRO11048  
Figure 1286: DNA324394, XM\_042168,  
gen.XM\_042168  
Figure 1287: PRO81059  
Figure 1288A-B: DNA324395, XM\_114356,  
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Figure 1289: DNA324396, XM\_105236,  
gen.XM\_105236  
Figure 1290: DNA324397, XM\_010978,  
gen.XM\_010978  
Figure 1291: DNA324398, XM\_017356,  
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Figure 1292A-B: DNA324399, XM\_039796,

gen.XM\_039796  
Figure 1293: PRO81064  
Figure 1294: DNA324400, XM\_016334,  
gen.XM\_016334  
Figure 1295: DNA324401, XM\_116058,  
gen.XM\_116058  
Figure 1296: DNA324402, XM\_113408,  
gen.XM\_113408  
Figure 1297: DNA324403, NM\_002492,  
gen.NM\_002492  
Figure 1298: PRO81068  
Figure 1299: DNA324404, XM\_037381,  
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Figure 1300: DNA324405, XM\_037377,  
gen.XM\_037377  
Figure 1301: PRO69681  
Figure 1302A-B: DNA324406, XM\_087254,  
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Figure 1303: PRO81070  
Figure 1304: DNA324407, XM\_037600,  
gen.XM\_037600  
Figure 1305: PRO81071  
Figure 1306: DNA324408, NM\_018023,  
gen.NM\_018023  
Figure 1307: PRO81072  
Figure 1308: DNA324409, XM\_093423,  
gen.XM\_093423  
Figure 1309: PRO81073  
Figure 1310: DNA324410, XM\_029136,  
gen.XM\_029136  
Figure 1311: PRO81074  
Figure 1312: DNA324411, XM\_087322,  
gen.XM\_087322  
Figure 1313A-B: DNA324412, XM\_029132,  
gen.XM\_029132  
Figure 1314A-B: DNA324413, XM\_029104,  
gen.XM\_029104  
Figure 1315: DNA324414, XM\_084120,  
gen.XM\_084120  
Figure 1316: DNA254620, NM\_005787,  
gen.NM\_005787  
Figure 1317: PRO49722  
Figure 1318: DNA324415, NM\_032331,  
gen.NM\_032331  
Figure 1319: PRO81079  
Figure 1320: DNA324416, XM\_011074,  
gen.XM\_011074  
Figure 1321: PRO81080  
Figure 1322: DNA324417, XM\_087295,  
gen.XM\_087295  
Figure 1323: DNA324418, XM\_087289,  
gen.XM\_087289  
Figure 1324: PRO81082  
Figure 1325: DNA324419, XM\_105658,  
gen.XM\_105658  
Figure 1326: PRO81083

Figure 1327: DNA89239, NM\_000893,  
gen.NM\_000893  
Figure 1328: PRO2906  
Figure 1329: DNA324420, XM\_113422,  
gen.XM\_113422  
Figure 1330: DNA225592, NM\_001622,  
gen.NM\_001622  
Figure 1331: PRO36055  
Figure 1332: DNA324421, XM\_005180,  
gen.XM\_005180  
Figure 1333: DNA324422, XM\_087392,  
gen.XM\_087392  
Figure 1334: PRO81086  
Figure 1335A-B: DNA272605, NM\_003722,  
gen.NM\_003722  
Figure 1336: PRO60741  
Figure 1337: DNA324423, XM\_117311,  
gen.XM\_117311  
Figure 1338: DNA324424, XM\_116034,  
gen.XM\_116034  
Figure 1339: PRO81088  
Figure 1340A-B: DNA324425, XM\_084110,  
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Figure 1341: DNA324426, XM\_038243,  
gen.XM\_038243  
Figure 1342: PRO81090  
Figure 1343: DNA324427, XM\_087359,  
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Figure 1344: DNA324428, XM\_114328,  
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Figure 1345: DNA324429, XM\_098109,  
gen.XM\_098109  
Figure 1346: PRO81093  
Figure 1347: DNA324430, XM\_087410,  
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Figure 1348: DNA324431, NM\_033316,  
gen.NM\_033316  
Figure 1349: PRO81095  
Figure 1350: DNA324432, XM\_166017,  
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Figure 1351: PRO81096  
Figure 1352: DNA79129, NM\_001647,  
gen.NM\_001647  
Figure 1353: PRO2551  
Figure 1354: DNA324433, NM\_032288,  
gen.NM\_032288  
Figure 1355: PRO81097  
Figure 1356: DNA324434, XM\_086228,  
gen.XM\_086228  
Figure 1357: PRO81098  
Figure 1358: DNA324435, XM\_087278,  
gen.XM\_087278  
Figure 1359: DNA324436, XM\_018523,  
gen.XM\_018523  
Figure 1360: DNA324437, XM\_087297,  
gen.XM\_087297

Figure 1361: DNA324438, XM\_002255,  
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Figure 1362: PRO81102  
Figure 1363: DNA324439, XM\_053122,  
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Figure 1364: DNA324440, XM\_042695,  
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Figure 1365: DNA324441, XM\_011160,  
gen.XM\_011160  
Figure 1366: DNA324442, NM\_007100,  
gen.NM\_007100  
Figure 1367: PRO81106  
Figure 1368: DNA139747, NM\_002477,  
gen.NM\_002477  
Figure 1369: PRO9785  
Figure 1370: DNA253804, NM\_032219,  
gen.NM\_032219  
Figure 1371: PRO49209  
Figure 1372: DNA324443, NM\_138385,  
gen.NM\_138385  
Figure 1373: PRO81107  
Figure 1374: DNA324444, NM\_006342,  
gen.NM\_006342  
Figure 1375: PRO81108  
Figure 1376A-C: DNA324445, NM\_133330,  
gen.NM\_133330  
Figure 1377: PRO81109  
Figure 1378A-C: DNA324446, NM\_014919,  
gen.NM\_014919  
Figure 1379: PRO81110  
Figure 1380A-C: DNA324447, NM\_133332,  
gen.NM\_133332  
Figure 1381: PRO81111  
Figure 1382: DNA324448, NM\_005663,  
gen.NM\_005663  
Figure 1383: PRO81112  
Figure 1384A-B: DNA324449, XM\_098248,  
gen.XM\_098248  
Figure 1385: PRO81113  
Figure 1386: DNA270615, NM\_002938,  
gen.NM\_002938  
Figure 1387: PRO58986  
Figure 1388A-B: DNA324450, NM\_014190,  
gen.NM\_014190  
Figure 1389: PRO81114  
Figure 1390A-B: DNA324451, NM\_014189,  
gen.NM\_014189  
Figure 1391: PRO81115  
Figure 1392: DNA324452, XM\_035572,  
gen.XM\_035572  
Figure 1393: PRO81116  
Figure 1394A-B: DNA324453, NM\_014556,  
gen.NM\_014556  
Figure 1395: PRO81117  
Figure 1396: DNA324454, NM\_001313,  
gen.NM\_001313

Figure 1397: PRO60542  
Figure 1398A-B: DNA324455, XM\_052626,  
gen.XM\_052626  
Figure 1399: PRO81118  
Figure 1400: DNA324456, NM\_016930,  
gen.NM\_016930  
Figure 1401: PRO81119  
Figure 1402: DNA324457, XM\_035824,  
gen.XM\_035824  
Figure 1403: PRO81120  
Figure 1404: DNA324458, NM\_033296,  
gen.NM\_033296  
Figure 1405: PRO81121  
Figure 1406: DNA324459, NM\_138699,  
gen.NM\_138699  
Figure 1407: PRO81122  
Figure 1408: DNA324460, XM\_116285,  
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Figure 1409: PRO81123  
Figure 1410: DNA324461, XM\_041221,  
gen.XM\_041221  
Figure 1411: PRO81124  
Figure 1412: DNA324462, XM\_117351,  
gen.XM\_117351  
Figure 1413: DNA324463, XM\_039165,  
gen.XM\_039165  
Figure 1414: DNA324464, NM\_025205,  
gen.NM\_025205  
Figure 1415: PRO81127  
Figure 1416: DNA324465, XM\_039173,  
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Figure 1417: DNA324466, XM\_039176,  
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Figure 1418: DNA324467, XM\_087583,  
gen.XM\_087583  
Figure 1419: DNA324468, NM\_017491,  
gen.NM\_017491  
Figure 1420: PRO12077  
Figure 1421: DNA324469, NM\_005112,  
gen.NM\_005112  
Figure 1422: PRO81131  
Figure 1423: DNA324470, XM\_011129,  
gen.XM\_011129  
Figure 1424A-B: DNA324471, XM\_052530,  
gen.XM\_052530  
Figure 1425: DNA324472, NM\_000661,  
gen.NM\_000661  
Figure 1426: PRO81134  
Figure 1427A-B: DNA324473, NM\_002913,  
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Figure 1428: PRO81135  
Figure 1429A-B: DNA324474, XM\_047477,  
gen.XM\_047477  
Figure 1430: DNA324475, NM\_004181,  
gen.NM\_004181  
Figure 1431: PRO81137

Figure 1432: DNA324476, XM\_003435,  
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Figure 1433: DNA324478, XM\_010941,  
gen.XM\_010941  
Figure 1434: DNA324479, XM\_059593,  
gen.XM\_059593  
Figure 1435: DNA324480, NM\_001553,  
gen.NM\_001553  
Figure 1436: PRO81141  
Figure 1437: DNA327511, NM\_032313,  
gen.NM\_032313  
Figure 1438: PRO52083  
Figure 1439: DNA324481, XM\_071623,  
gen.XM\_071623  
Figure 1440A-B: DNA324482, XM\_036002,  
gen.XM\_036002  
Figure 1441: DNA324483, XM\_058927,  
gen.XM\_058927  
Figure 1442: DNA324484, XM\_059628,  
gen.XM\_059628  
Figure 1443: DNA324485, XM\_046057,  
gen.XM\_046057  
Figure 1444: PRO81146  
Figure 1445: DNA324486, XM\_031320,  
gen.XM\_031320  
Figure 1446: DNA225919, NM\_001134,  
gen.NM\_001134  
Figure 1447: PRO36382  
Figure 1448A-B: DNA324487, XM\_003511,  
gen.XM\_003511  
Figure 1449: DNA324488, NM\_006835,  
gen.NM\_006835  
Figure 1450: PRO4605  
Figure 1451: DNA324489, XM\_003305,  
gen.XM\_003305  
Figure 1452: DNA324490, XM\_113425,  
gen.XM\_113425  
Figure 1453: DNA324491, XM\_001389,  
gen.XM\_001389  
Figure 1454: PRO81148  
Figure 1455: DNA324492, XM\_087527,  
gen.XM\_087527  
Figure 1456: DNA324493, XM\_035986,  
gen.XM\_035986  
Figure 1457A-B: DNA324494, NM\_014933,  
gen.NM\_014933  
Figure 1458: PRO81150  
Figure 1459: DNA290585, NM\_000582,  
gen.NM\_000582  
Figure 1460: PRO70536  
Figure 1461: DNA324495, XM\_055551,  
gen.XM\_055551  
Figure 1462: PRO81151  
Figure 1463: DNA324496, XM\_087498,  
gen.XM\_087498  
Figure 1464: DNA324497, XM\_096203,

gen.XM\_096203  
Figure 1465: DNA324498, XM\_084158,  
gen.XM\_084158  
Figure 1466: DNA324499, XM\_034710,  
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Figure 1467: PRO81156  
Figure 1468: DNA324500, XM\_034713,  
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Figure 1469: DNA324501, XM\_059633,  
gen.XM\_059633  
Figure 1470: DNA324502, XM\_114426,  
gen.XM\_114426  
Figure 1471: DNA324503, XM\_056957,  
gen.XM\_056957  
Figure 1472: DNA324504, XM\_088472,  
gen.XM\_088472  
Figure 1473: DNA324505, XM\_114424,  
gen.XM\_114424  
Figure 1474A-B: DNA324506, XM\_042301,  
gen.XM\_042301  
Figure 1475: PRO81163  
Figure 1476: DNA324507, XM\_017925,  
gen.XM\_017925  
Figure 1477: DNA324508, XM\_052336,  
gen.XM\_052336  
Figure 1478: DNA324509, NM\_002106,  
gen.NM\_002106  
Figure 1479: PRO10297  
Figure 1480: DNA324510, XM\_085068,  
gen.XM\_085068  
Figure 1481: PRO81166  
Figure 1482: DNA324511, XM\_165473,  
gen.XM\_165473  
Figure 1483: DNA324512, XM\_087514,  
gen.XM\_087514  
Figure 1484: DNA324513, XM\_116247,  
gen.XM\_116247  
Figure 1485: DNA324514, NM\_002358,  
gen.NM\_002358  
Figure 1486: PRO81169  
Figure 1487: DNA324515, XM\_050200,  
gen.XM\_050200  
Figure 1488: PRO81170  
Figure 1489: DNA225584, NM\_001154,  
gen.NM\_001154  
Figure 1490: PRO36047  
Figure 1491: DNA324516, NM\_024900,  
gen.NM\_024900  
Figure 1492: PRO81171  
Figure 1493: DNA324517, XM\_040752,  
gen.XM\_040752  
Figure 1494: DNA324518, NM\_002413,  
gen.NM\_002413  
Figure 1495: PRO60956  
Figure 1496: DNA324519, XM\_114401,  
gen.XM\_114401

Figure 1497: DNA324520, XM\_068164, gen.XM\_068164  
Figure 1498: PRO81174  
Figure 1499: DNA324521, XM\_060067, gen.XM\_060067  
Figure 1500: DNA324522, XM\_003555, gen.XM\_003555  
Figure 1501: PRO81176  
Figure 1502: DNA324523, XM\_034321, gen.XM\_034321  
Figure 1503: PRO81177  
Figure 1504: DNA324524, NM\_006439, gen.NM\_006439  
Figure 1505: PRO81178  
Figure 1506: DNA324525, NM\_001006, gen.NM\_001006  
Figure 1507: PRO81179  
Figure 1508: DNA227575, NM\_005141, gen.NM\_005141  
Figure 1509: PRO38038  
Figure 1510: DNA324526, XM\_114368, gen.XM\_114368  
Figure 1511A-B: DNA225920, NM\_000508, gen.NM\_000508  
Figure 1512: PRO36383  
Figure 1513: DNA324527, NM\_021871, gen.NM\_021871  
Figure 1514: PRO81181  
Figure 1515: DNA225921, NM\_000509, gen.NM\_000509  
Figure 1516: PRO36384  
Figure 1517: DNA324528, NM\_021870, gen.NM\_021870  
Figure 1518: PRO81182  
Figure 1519: DNA324529, XM\_059623, gen.XM\_059623  
Figure 1520: DNA324530, XM\_106246, gen.XM\_106246  
Figure 1521: PRO81184  
Figure 1522: DNA324531, NM\_002129, gen.NM\_002129  
Figure 1523: PRO81185  
Figure 1524: DNA324532, XM\_040321, gen.XM\_040321  
Figure 1525: DNA324533, XM\_015563, gen.XM\_015563  
Figure 1526: DNA324534, NM\_024748, gen.NM\_024748  
Figure 1527: PRO81188  
Figure 1528: DNA324535, XM\_165470, gen.XM\_165470  
Figure 1529: PRO81189  
Figure 1530A-E: DNA324536, XM\_003477, gen.XM\_003477  
Figure 1531: DNA324537, XM\_165465, gen.XM\_165465

Figure 1532: DNA324538, XM\_116204, gen.XM\_116204  
Figure 1533: DNA324539, XM\_116205, gen.XM\_116205  
Figure 1534: DNA324540, XM\_098405, gen.XM\_098405  
Figure 1535: DNA324541, XM\_052313, gen.XM\_052313  
Figure 1536: PRO81195  
Figure 1537: DNA324542, XM\_087659, gen.XM\_087659  
Figure 1538: PRO81196  
Figure 1539: DNA324543, XM\_029096, gen.XM\_029096  
Figure 1540: DNA324544, XM\_003825, gen.XM\_003825  
Figure 1541: DNA324545, XM\_057994, gen.XM\_057994  
Figure 1542: PRO81199  
Figure 1543: DNA324546, XM\_087686, gen.XM\_087686  
Figure 1544: DNA324547, XM\_017641, gen.XM\_017641  
Figure 1545: DNA324548, NM\_030782, gen.NM\_030782  
Figure 1546: PRO81202  
Figure 1547: DNA324549, XM\_084168, gen.XM\_084168  
Figure 1548: DNA324550, XM\_057492, gen.XM\_057492  
Figure 1549: DNA324551, XM\_087597, gen.XM\_087597  
Figure 1550: DNA324552, XM\_087601, gen.XM\_087601  
Figure 1551: DNA324554, XM\_087599, gen.XM\_087599  
Figure 1552: DNA324555, XM\_114435, gen.XM\_114435  
Figure 1553: DNA324556, XM\_087600, gen.XM\_087600  
Figure 1554: DNA324557, XM\_016170, gen.XM\_016170  
Figure 1555: DNA324558, XM\_114434, gen.XM\_114434  
Figure 1556: DNA324559, XM\_113452, gen.XM\_113452  
Figure 1557: DNA324560, XM\_071580, gen.XM\_071580  
Figure 1558: PRO81213  
Figure 1559: DNA324561, XM\_087713, gen.XM\_087713  
Figure 1560: PRO81214  
Figure 1561: DNA324562, XM\_094440, gen.XM\_094440  
Figure 1562: DNA324563, XM\_106739, gen.XM\_106739

Figure 1563: PRO81216  
Figure 1564: DNA324564, XM\_087614,  
gen.XM\_087614  
Figure 1565: DNA324565, XM\_004009,  
gen.XM\_004009  
Figure 1566: PRO81219  
Figure 1567: DNA324566, XM\_114437,  
gen.XM\_114437  
Figure 1568: DNA324567, XM\_043771,  
gen.XM\_043771  
Figure 1569: PRO81221  
Figure 1570: DNA324568, NM\_000997,  
gen.NM\_000997  
Figure 1571: PRO11077  
Figure 1572: DNA324569, XM\_003869,  
gen.XM\_003869  
Figure 1573: DNA227173, NM\_001465,  
gen.NM\_001465  
Figure 1574: PRO37636  
Figure 1575: DNA324570, NM\_018034,  
gen.NM\_018034  
Figure 1576: PRO81223  
Figure 1577: DNA324571, NM\_032637,  
gen.NM\_032637  
Figure 1578: PRO81224  
Figure 1579: DNA324572, NM\_005983,  
gen.NM\_005983  
Figure 1580: PRO81225  
Figure 1581A-B: DNA324573, XM\_003896,  
gen.XM\_003896  
Figure 1582: DNA287282, NM\_002130,  
gen.NM\_002130  
Figure 1583: PRO69554  
Figure 1584: DNA324574, XM\_114442,  
gen.XM\_114442  
Figure 1585: PRO81227  
Figure 1586: DNA324575, XM\_114439,  
gen.XM\_114439  
Figure 1587: DNA324576, XM\_114440,  
gen.XM\_114440  
Figure 1588A-B: DNA324577, XM\_032902,  
gen.XM\_032902  
Figure 1589: PRO81230  
Figure 1590: DNA324578, XM\_032895,  
gen.XM\_032895  
Figure 1591: DNA324579, XM\_084179,  
gen.XM\_084179  
Figure 1592: DNA324580, XM\_041712,  
gen.XM\_041712  
Figure 1593: DNA324581, XM\_116439,  
gen.XM\_116439  
Figure 1594: PRO81234  
Figure 1595: DNA324582, XM\_087611,  
gen.XM\_087611  
Figure 1596: DNA324583, XM\_059653,  
gen.XM\_059653

Figure 1597: DNA324584, XM\_087610,  
gen.XM\_087610  
Figure 1598: DNA288259, NM\_031966,  
gen.NM\_031966  
Figure 1599: PRO4676  
Figure 1600: DNA324585, XM\_042025,  
gen.XM\_042025  
Figure 1601: PRO81238  
Figure 1602: DNA324586, NM\_005713,  
gen.NM\_005713  
Figure 1603: PRO81239  
Figure 1604: DNA324587, XM\_059709,  
gen.XM\_059709  
Figure 1605: PRO81240  
Figure 1606: DNA324588, XM\_116447,  
gen.XM\_116447  
Figure 1607: PRO81241  
Figure 1608: DNA324589, XM\_037260,  
gen.XM\_037260  
Figure 1609: DNA324590, XM\_098351,  
gen.XM\_098351  
Figure 1610: DNA324591, XM\_098354,  
gen.XM\_098354  
Figure 1611: DNA324592, XM\_098352,  
gen.XM\_098352  
Figure 1612: DNA324593, XM\_166037,  
gen.XM\_166037  
Figure 1613: PRO81246  
Figure 1614: DNA324594, XM\_041694,  
gen.XM\_041694  
Figure 1615: DNA324595, XM\_165488,  
gen.XM\_165488  
Figure 1616: PRO81248  
Figure 1617: DNA324596, XM\_059669,  
gen.XM\_059669  
Figure 1618: PRO81249  
Figure 1619: DNA324597, XM\_027964,  
gen.XM\_027964  
Figure 1620: PRO81250  
Figure 1621: DNA324598, XM\_088020,  
gen.XM\_088020  
Figure 1622: DNA324599, XM\_117387,  
gen.XM\_117387  
Figure 1623: DNA324600, XM\_114469,  
gen.XM\_114469  
Figure 1624: DNA324601, NM\_001207,  
gen.NM\_001207  
Figure 1625: PRO22771  
Figure 1626A-B: DNA324602, XM\_032553,  
gen.XM\_032553  
Figure 1627: DNA254147, NM\_000521,  
gen.NM\_000521  
Figure 1628: PRO49262  
Figure 1629: DNA324603, NM\_031482,  
gen.NM\_031482  
Figure 1630: PRO81254

Figure 1631: DNA324604, XM\_087790,  
gen.XM\_087790  
Figure 1632: DNA324605, NM\_001025,  
gen.NM\_001025  
Figure 1633: PRO10685  
Figure 1634: DNA324606, XM\_098362,  
gen.XM\_098362  
Figure 1635: PRO81256  
Figure 1636: DNA324607, NM\_003401,  
gen.NM\_003401  
Figure 1637: PRO70327  
Figure 1638: DNA290231, NM\_022550,  
gen.NM\_022550  
Figure 1639: PRO70327  
Figure 1640: DNA324608, XM\_017857,  
gen.XM\_017857  
Figure 1641: DNA324609, XM\_117398,  
gen.XM\_117398  
Figure 1642A-B: DNA257253, NM\_032280,  
gen.NM\_032280  
Figure 1643: PRO51851  
Figure 1644: DNA324610, XM\_003771,  
gen.XM\_003771  
Figure 1645: PRO81259  
Figure 1646A-B: DNA269816, NM\_002397,  
gen.NM\_002397  
Figure 1647: PRO58219  
Figure 1648: DNA324611, XM\_116427,  
gen.XM\_116427  
Figure 1649: PRO81260  
Figure 1650: DNA324612, NM\_004772,  
gen.NM\_004772  
Figure 1651: PRO81261  
Figure 1652: DNA324613, XM\_016674,  
gen.XM\_016674  
Figure 1653: PRO81262  
Figure 1654: DNA324614, XM\_113463,  
gen.XM\_113463  
Figure 1655: DNA324615, XM\_034744,  
gen.XM\_034744  
Figure 1656: DNA324616, XM\_087745,  
gen.XM\_087745  
Figure 1657: PRO81264  
Figure 1658: DNA324617, XM\_018473,  
gen.XM\_018473  
Figure 1659: PRO81265  
Figure 1660: DNA324618, XM\_087635,  
gen.XM\_087635  
Figure 1661: PRO81266  
Figure 1662: DNA324619, XM\_087637,  
gen.XM\_087637  
Figure 1663: DNA324620, XM\_166027,  
gen.XM\_166027  
Figure 1664: DNA324621, NM\_014035,  
gen.NM\_014035  
Figure 1665: PRO1285

Figure 1666: DNA324622, XM\_003830,  
gen.XM\_003830  
Figure 1667: PRO81269  
Figure 1668: DNA324623, XM\_037002,  
gen.XM\_037002  
Figure 1669: DNA324624, XM\_166026,  
gen.XM\_166026  
Figure 1670: DNA324625, XM\_041059,  
gen.XM\_041059  
Figure 1671: DNA83020, NM\_000358,  
gen.NM\_000358  
Figure 1672: PRO2561  
Figure 1673: DNA324626, NM\_003687,  
gen.NM\_003687  
Figure 1674: PRO81272  
Figure 1675: DNA324627, XM\_034862,  
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Figure 1676: PRO34544  
Figure 1677: DNA103380, NM\_003374,  
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Figure 1678: PRO4710  
Figure 1679: DNA324628, XM\_017474,  
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Figure 1680: PRO63082  
Figure 1681A-B: DNA324629, NM\_014829,  
gen.NM\_014829  
Figure 1682: PRO81273  
Figure 1683A-B: DNA324630, XM\_114482,  
gen.XM\_114482  
Figure 1684: PRO81274  
Figure 1685: DNA324631, NM\_004893,  
gen.NM\_004893  
Figure 1686: PRO81275  
Figure 1687: DNA269809, NM\_006805,  
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Figure 1688: PRO58213  
Figure 1689: DNA226872, NM\_001964,  
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Figure 1690: PRO37335  
Figure 1691: DNA324632, XM\_116307,  
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Figure 1692: PRO81276  
Figure 1693: DNA324633, NM\_004134,  
gen.NM\_004134  
Figure 1694: PRO81277  
Figure 1695: DNA324634, XM\_038221,  
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Figure 1696: PRO81278  
Figure 1697: DNA271931, NM\_005754,  
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Figure 1698: PRO60207  
Figure 1699: DNA324635, XM\_003841,  
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Figure 1700: DNA324636, XM\_032759,  
gen.XM\_032759  
Figure 1701: DNA324637, XM\_017591,



gen.XM\_017591  
Figure 1702: DNA324638, NM\_006058,  
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Figure 1703: PRO81280  
Figure 1704: DNA324639, NM\_002084,  
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Figure 1705: PRO81281  
Figure 1706: DNA324640, NM\_018047,  
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Figure 1707: PRO81282  
Figure 1708: DNA324641, NM\_005617,  
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Figure 1709: PRO10849  
Figure 1710: DNA324642, XM\_003937,  
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Figure 1711: DNA324643, XM\_087621,  
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Figure 1712A-B: DNA324644, XM\_003789,  
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Figure 1713: DNA324645, XM\_087652,  
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Figure 1714: DNA324646, XM\_068853,  
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Figure 1715: PRO81286  
Figure 1716: DNA324647, XM\_116465,  
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Figure 1717: PRO81287  
Figure 1718: DNA3202020, NM\_005573,  
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Figure 1719: PRO70993  
Figure 1720: DNA324648, XM\_113467,  
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Figure 1721: DNA271626, NM\_014773,  
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Figure 1722: PRO59913  
Figure 1723A-B: DNA324649, XM\_056315,  
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Figure 1724: DNA324650, NM\_024668,  
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Figure 1726: DNA324651, NM\_080670,  
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Figure 1727: PRO81290  
Figure 1728A-B: DNA324652, NM\_002588,  
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Figure 1729: PRO81291  
Figure 1730A-B: DNA324653, NM\_003735,  
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Figure 1731: PRO81292  
Figure 1732A-B: DNA150679, NM\_003736,  
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Figure 1733: PRO12416  
Figure 1734A-B: DNA324654, NM\_018912,  
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Figure 1735: PRO36058  
Figure 1736A-B: DNA324655, NM\_018913,

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Figure 1737: PRO81293  
Figure 1738A-B: DNA324656, NM\_018914,  
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Figure 1739: PRO81294  
Figure 1740A-B: DNA324657, NM\_018915,  
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Figure 1741: PRO36020  
Figure 1742A-B: DNA324658, NM\_018916,  
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Figure 1743: PRO81295  
Figure 1744A-B: DNA324659, NM\_018917,  
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Figure 1745: PRO81296  
Figure 1746A-B: DNA324660, NM\_018918,  
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Figure 1747: PRO81297  
Figure 1748A-B: DNA324661, NM\_018919,  
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Figure 1749: PRO81298  
Figure 1750A-B: DNA324662, NM\_018920,  
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Figure 1751: PRO81299  
Figure 1752A-B: DNA324663, NM\_018921,  
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Figure 1753: PRO81300  
Figure 1754A-B: DNA324664, NM\_018922,  
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Figure 1755: PRO81301  
Figure 1756A-B: DNA324665, NM\_018923,  
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Figure 1757: PRO81302  
Figure 1758A-B: DNA324666, NM\_018924,  
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Figure 1759: PRO81303  
Figure 1760A-B: DNA324667, NM\_018925,  
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Figure 1761: PRO81304  
Figure 1762A-B: DNA324668, NM\_018926,  
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Figure 1763: PRO81305  
Figure 1764A-B: DNA324669, NM\_018927,  
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Figure 1765: PRO37091  
Figure 1766A-B: DNA324670, NM\_018928,  
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Figure 1767: PRO81306  
Figure 1768A-B: DNA324671, NM\_018929,  
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Figure 1769: PRO81307  
Figure 1770A-B: DNA324672, NM\_032088,  
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Figure 1771: PRO81308  
Figure 1772A-B: DNA324673, NM\_032092,  
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Figure 1773: PRO81309

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Figure 1775: PRO81310  
Figure 1776: DNA324675, NM\_032402,  
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Figure 1777: PRO81311  
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Figure 1779: DNA324677, NM\_002109,  
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Figure 1780: PRO4908  
Figure 1781: DNA324678, XM\_084180,  
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Figure 1782: PRO81313  
Figure 1783: DNA324679, XM\_039975,  
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Figure 1784: PRO81314  
Figure 1785: DNA324680, NM\_033551,  
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Figure 1786: PRO81315  
Figure 1787: DNA324681, NM\_004821,  
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Figure 1788: PRO81316  
Figure 1789: DNA324682, XM\_068395,  
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Figure 1790: PRO81317  
Figure 1791: DNA226418, NM\_004060,  
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Figure 1792: PRO36881  
Figure 1793A-B: DNA324683, XM\_056963,  
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Figure 1794: PRO81318  
Figure 1795: DNA324684, NM\_004219,  
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Figure 1796: PRO81319  
Figure 1797: DNA324685, XM\_094243,  
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Figure 1799: DNA324687, XM\_016345,  
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Figure 1803: DNA324690, NM\_002520,  
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Figure 1804: PRO58993  
Figure 1805: DNA324691, XM\_043340,  
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Figure 1806: PRO81325  
Figure 1807: DNA324692, XM\_116340,  
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Figure 1808A-B: DNA324693, XM\_043388,  
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Figure 1809: PRO81327  
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Figure 1811: DNA324695, XM\_003716,  
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Figure 1812: DNA227320, NM\_003714,  
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Figure 1813: PRO37783  
Figure 1814: DNA324696, NM\_032361,  
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Figure 1815: PRO81330  
Figure 1816: DNA324697, XM\_087773,  
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Figure 1817: DNA324698, XM\_114457,  
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Figure 1818: DNA324699, XM\_165483,  
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Figure 1819: DNA324700, XM\_114453,  
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Figure 1820: DNA324701, XM\_165484,  
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Figure 1821: DNA324702, XM\_030771,  
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Figure 1822: PRO19615  
Figure 1823: DNA324703, XM\_030777,  
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Figure 1824: DNA324704, XM\_030782,  
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Figure 1825: PRO81336  
Figure 1826: DNA324705, NM\_030567,  
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Figure 1827: PRO81337  
Figure 1828: DNA225909, NM\_000505,  
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Figure 1829: PRO36372  
Figure 1830: DNA274206, NM\_006816,  
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Figure 1831: PRO62135  
Figure 1832: DNA324706, NM\_031300,  
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Figure 1833: PRO81338  
Figure 1834: DNA324707, NM\_013237,  
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Figure 1835: PRO81339  
Figure 1836: DNA324708, NM\_002011,  
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Figure 1837: PRO81340  
Figure 1838: DNA324709, NM\_022963,  
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Figure 1839: PRO81341  
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Figure 1841: DNA324711, XM\_113454,  
gen.XM\_113454  
Figure 1842: DNA324712, XM\_166028,  
gen.XM\_166028

Figure 1843: DNA324713, NM\_015043,  
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Figure 1844: PRO81345  
Figure 1845: DNA324714, XM\_113468,  
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Figure 1846: DNA324715, NM\_014275,  
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Figure 1847: PRO1927  
Figure 1848: DNA324716, NM\_054013,  
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Figure 1849: PRO81347  
Figure 1850: DNA270675, NM\_005520,  
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Figure 1851: PRO59040  
Figure 1852: DNA324717, NM\_006098,  
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Figure 1853: PRO25849  
Figure 1854: DNA269593, NM\_005110,  
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Figure 1855: PRO58006  
Figure 1856: DNA324718, XM\_116365,  
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Figure 1857: DNA324719, XM\_116511,  
gen.XM\_116511  
Figure 1858: DNA324720, XM\_087823,  
gen.XM\_087823  
Figure 1859A-C: DNA324721, XM\_053955,  
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Figure 1860: DNA324722, XM\_113476,  
gen.XM\_113476  
Figure 1861: DNA324723, XM\_116514,  
gen.XM\_116514  
Figure 1862: DNA324724, XM\_094741,  
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Figure 1863: DNA324725, NM\_025168,  
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Figure 1864: PRO81354  
Figure 1865A-B: DNA324726, XM\_165740,  
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Figure 1866: DNA272171, NM\_002388,  
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Figure 1867: PRO60438  
Figure 1868: DNA324727, XM\_167169,  
gen.XM\_167169  
Figure 1869: PRO81355  
Figure 1870: DNA324728, NM\_014452,  
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Figure 1871: PRO868  
Figure 1872: DNA324729, XM\_166349,  
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Figure 1873: PRO81356  
Figure 1874: DNA304680, NM\_007355,  
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Figure 1875: PRO71106  
Figure 1876: DNA324730, XM\_165772,  
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Figure 1877: DNA324731, XM\_168123,  
gen.XM\_168123  
Figure 1878: DNA324732, XM\_166457,  
gen.XM\_166457  
Figure 1879: DNA324733, XM\_166469,  
gen.XM\_166469  
Figure 1880: DNA324734, NM\_018135,  
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Figure 1881: PRO81359  
Figure 1882A-B: DNA324735, XM\_166340,  
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Figure 1883: DNA324736, XM\_087960,  
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Figure 1884: DNA324737, XM\_166362,  
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Figure 1885: PRO81362  
Figure 1886: DNA227204, NM\_015388,  
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Figure 1887: PRO37667  
Figure 1888: DNA324738, XM\_166425,  
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Figure 1889: PRO81363  
Figure 1890: DNA324739, NM\_057161,  
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Figure 1891: PRO81364  
Figure 1892: DNA270613, NM\_006245,  
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Figure 1893: PRO58984  
Figure 1894: DNA324740, NM\_006586,  
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Figure 1895: PRO81365  
Figure 1896: DNA324741, XM\_166402,  
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Figure 1897: PRO81366  
Figure 1898: DNA324742, NM\_001760,  
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Figure 1899: PRO81367  
Figure 1900: DNA287246, NM\_004053,  
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Figure 1901: PRO69521  
Figure 1902: DNA324743, NM\_017601,  
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Figure 1903: PRO81368  
Figure 1904: DNA275630, NM\_006708,  
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Figure 1905: PRO63253  
Figure 1906: DNA324744, NM\_014341,  
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Figure 1907: PRO81369  
Figure 1908: DNA304460, NM\_016059,  
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Figure 1909: PRO4984  
Figure 1910: DNA324745, XM\_166412,  
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Figure 1911: PRO81370  
Figure 1912: DNA304716, NM\_078467,

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Figure 1913: PRO71142  
Figure 1914: DNA324746, XM.166417,  
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Figure 1915: PRO81371  
Figure 1916A-B: DNA324747, NM.003137,  
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Figure 1917: PRO81372  
Figure 1918A-B: DNA324748, NM.004117,  
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Figure 1919: PRO36841  
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Figure 1921: DNA324750, XM.165794,  
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Figure 1922: DNA324751, NM.007104,  
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Figure 1923: PRO10360  
Figure 1924: DNA324752, NM.024294,  
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Figure 1925: PRO81375  
Figure 1926: DNA324753, NM.022758,  
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Figure 1927: PRO50582  
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Figure 1930: PRO81377  
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Figure 1933: PRO81379  
Figure 1934: DNA324758, XM.058039,  
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Figure 1935: PRO81380  
Figure 1936: DNA324759, XM.087990,  
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Figure 1937: DNA324760, XM.165743,  
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Figure 1938: DNA324761, XM.166360,  
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Figure 1939: DNA324763, XM.059801,  
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Figure 1941: DNA324765, XM.016857,  
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Figure 1942: DNA227442, NM.001350,  
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Figure 1943: PRO37905  
Figure 1944: DNA324766, NM.005452,  
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Figure 1945: PRO81387  
Figure 1946: DNA304661, NM.022551,

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Figure 1947: PRO71088  
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Figure 1949: DNA324768, XM.165698,  
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Figure 1950: PRO4884  
Figure 1951A-B: DNA324769, XM.165770,  
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Figure 1952: DNA287227, NM.004159,  
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Figure 1953: PRO69506  
Figure 1954: DNA324770, XM.165717,  
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Figure 1955: DNA324771, XM.166480,  
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Figure 1956: DNA324772, XM.165801,  
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Figure 1957A-B: DNA324773, NM.000592,  
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Figure 1958: PRO36316  
Figure 1959: DNA324774, NM.001710,  
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Figure 1960: PRO36305  
Figure 1961: DNA227607, NM.005346,  
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Figure 1962: PRO38070  
Figure 1963: DNA304668, NM.005345,  
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Figure 1964: PRO71095  
Figure 1965: DNA324775, NM.021177,  
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Figure 1966: PRO81394  
Figure 1967A-B: DNA272263, NM.006295,  
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Figure 1968: PRO70138  
Figure 1969: DNA287319, NM.001288,  
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Figure 1970: PRO69584  
Figure 1971: DNA324776, NM.001320,  
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Figure 1972: PRO63052  
Figure 1973A-B: DNA324777, NM.004639,  
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Figure 1974: PRO81395  
Figure 1975A-B: DNA324778, NM.080703,  
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Figure 1976: PRO81396  
Figure 1977A-B: DNA324779, NM.080702,  
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Figure 1978: PRO81397  
Figure 1979A-B: DNA324780, NM.004638,  
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Figure 1980: PRO81398  
Figure 1981A-B: DNA324781, NM.080686,  
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Figure 1982: PRO81399  
Figure 1983: DNA324782, XM\_165771,  
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Figure 1985: PRO71125  
Figure 1986: DNA304699, NM\_004640,  
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Figure 1987: PRO71125  
Figure 1988: DNA324784, XM\_165765,  
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Figure 1989: PRO81400  
Figure 1990: DNA324785, XM\_087945,  
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Figure 1991: PRO81401  
Figure 1992: DNA324786, XM\_166381,  
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Figure 1993: PRO81402  
Figure 1994: DNA324787, XM\_168104,  
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Figure 1995: DNA324788, XM\_166401,  
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Figure 1996: PRO81404  
Figure 1997: DNA271040, NM\_001517,  
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Figure 1998: PRO59365  
Figure 1999A-B: DNA324789, XM\_165738,  
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Figure 2000: DNA324790, XM\_087939,  
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Figure 2001: PRO81406  
Figure 2002: DNA324791, XM\_166353,  
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Figure 2003: PRO1112  
Figure 2004A-B: DNA324792, XM\_166376,  
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Figure 2005: PRO81407  
Figure 2006A-B: DNA324793, XM\_165799,  
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Figure 2007: DNA290264, NM\_025263,  
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Figure 2008: PRO70393  
Figure 2009: DNA324794, XM\_166361,  
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Figure 2010: PRO81409  
Figure 2011: DNA324795, XM\_165764,  
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Figure 2012: PRO81410  
Figure 2013: DNA324796, XM\_165758,  
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Figure 2014: PRO81411  
Figure 2015: DNA324797, XM\_166406,  
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Figure 2016: DNA324798, XM\_165809,  
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Figure 2017: DNA324799, NM\_018950,

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Figure 2018: PRO81414  
Figure 2019: DNA324800, XM\_166392,  
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Figure 2020: PRO81415  
Figure 2021: DNA324801, XM\_166336,  
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Figure 2022: PRO81416  
Figure 2023: DNA324802, XM\_167128,  
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Figure 2024: PRO23797  
Figure 2025: DNA324803, XM\_167161,  
gen.XM\_167161  
Figure 2026: PRO81417  
Figure 2027: DNA324804, NM\_013375,  
gen.NM\_013375  
Figure 2028: PRO81418  
Figure 2029: DNA324805, NM\_007047,  
gen.NM\_007047  
Figure 2030: PRO81419  
Figure 2031: DNA324806, XM\_167179,  
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Figure 2032: DNA290785, NM\_003107,  
gen.NM\_003107  
Figure 2033: PRO70544  
Figure 2034: DNA150772, NM\_003472,  
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Figure 2035: PRO12797  
Figure 2036A-B: DNA324807, XM\_165728,  
gen.XM\_165728  
Figure 2037: DNA324808, XM\_165749,  
gen.XM\_165749  
Figure 2038: PRO81421  
Figure 2039A-B: DNA324809, NM\_004973,  
gen.NM\_004973  
Figure 2040: PRO81422  
Figure 2041: DNA324810, XM\_167196,  
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Figure 2042: DNA324811, XM\_166446,  
gen.XM\_166446  
Figure 2043: PRO81424  
Figure 2044A-C: DNA324812, XM\_165777,  
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Figure 2045: DNA324813, XM\_037875,  
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Figure 2046: PRO81426  
Figure 2047: DNA324814, XM\_167225,  
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Figure 2048: PRO81427  
Figure 2049: DNA324815, XM\_166357,  
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Figure 2050: DNA324816, NM\_001069,  
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Figure 2051: PRO81429  
Figure 2052: DNA324817, NM\_001500,  
gen.NM\_001500

Figure 2053: PRO81430  
 Figure 2054A-B: DNA324818, XM\_166042,  
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 Figure 2055: PRO51389  
 Figure 2056: DNA324819, XM\_052721,  
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 Figure 2057: DNA324820, XM\_165499,  
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 Figure 2058: DNA324821, XM\_114497,  
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 Figure 2059: DNA324822, XM\_011117,  
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 Figure 2060: DNA324823, XM\_094855,  
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 Figure 2062: DNA324824, XM\_059776,  
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 Figure 2063: PRO81436  
 Figure 2064: DNA324825, XM\_055641,  
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 Figure 2065: DNA324826, XM\_004151,  
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 Figure 2066: DNA324827, NM\_133645,  
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 Figure 2067: PRO81439  
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 Figure 2071: PRO4798  
 Figure 2072: DNA324830, XM\_068963,  
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 Figure 2073: PRO81441  
 Figure 2074: DNA324831, XM\_040623,  
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 Figure 2075: DNA324832, NM\_020320,  
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 Figure 2076: PRO81443  
 Figure 2077: DNA324833, NM\_014107,  
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 Figure 2078: PRO81444  
 Figure 2079A-B: DNA324834, XM\_084204,  
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 Figure 2080: DNA324835, XM\_017517,  
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 Figure 2081: DNA324836, NM\_032929,  
 gen.NM\_032929  
 Figure 2082: PRO81446  
 Figure 2083: DNA324837, XM\_003611,  
 gen.XM\_003611  
 Figure 2084: PRO81447  
 Figure 2085: DNA324838, XM\_068919,  
 gen.XM\_068919  
 Figure 2086: PRO81448

Figure 2087: DNA324839, XM\_167016,  
 gen.XM\_167016  
 Figure 2088: PRO81449  
 Figure 2089: DNA324840, XM\_087855,  
 gen.XM\_087855  
 Figure 2090: DNA324841, XM\_087853,  
 gen.XM\_087853  
 Figure 2091: DNA324842, XM\_165669,  
 gen.XM\_165669  
 Figure 2092: DNA324843, XM\_166303,  
 gen.XM\_166303  
 Figure 2093: PRO81453  
 Figure 2094: DNA324844, XM\_167027,  
 gen.XM\_167027  
 Figure 2095: PRO81454  
 Figure 2096: DNA324845, XM\_167037,  
 gen.XM\_167037  
 Figure 2097: PRO81455  
 Figure 2098: DNA324846, XM\_018182,  
 gen.XM\_018182  
 Figure 2099: DNA227924, NM\_000165,  
 gen.NM\_000165  
 Figure 2100: PRO38387  
 Figure 2101: DNA324847, XM\_166310,  
 gen.XM\_166310  
 Figure 2102: PRO81457  
 Figure 2103: DNA324848, XM\_168054,  
 gen.XM\_168054  
 Figure 2104: DNA271418, NM\_003287,  
 gen.NM\_003287  
 Figure 2105: PRO59717  
 Figure 2106: DNA324849, XM\_114492,  
 gen.XM\_114492  
 Figure 2107: DNA324850, XM\_037056,  
 gen.XM\_037056  
 Figure 2108: DNA324851, XM\_098468,  
 gen.XM\_098468  
 Figure 2109: PRO19933  
 Figure 2110: DNA324852, XM\_004526,  
 gen.XM\_004526  
 Figure 2111: DNA324853, NM\_001016,  
 gen.NM\_001016  
 Figure 2112: PRO81462  
 Figure 2113: DNA324854, XM\_004297,  
 gen.XM\_004297  
 Figure 2114: DNA324855, XM\_004256,  
 gen.XM\_004256  
 Figure 2115: PRO81464  
 Figure 2116: DNA324856, NM\_014320,  
 gen.NM\_014320  
 Figure 2117: PRO81465  
 Figure 2118: DNA324857, XM\_059741,  
 gen.XM\_059741  
 Figure 2119: DNA324858, XM\_017831,  
 gen.XM\_017831  
 Figure 2120: PRO81467

Figure 2121: DNA324859, XM\_049899,  
gen.XM\_049899  
Figure 2122: DNA324860, XM\_004379,  
gen.XM\_004379  
Figure 2123A-C: DNA324861, XM\_087834,  
gen.XM\_087834  
Figure 2124A-B: DNA324862, XM\_087836,  
gen.XM\_087836  
Figure 2125: PRO81471  
Figure 2126: DNA324863, NM\_005389,  
gen.NM\_005389  
Figure 2127: PRO66279  
Figure 2128A-C: DNA324864, XM\_029746,  
gen.XM\_029746  
Figure 2129: PRO66282  
Figure 2130: DNA324865, XM\_004383,  
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Figure 2131: DNA324866, XM\_059745,  
gen.XM\_059745  
Figure 2132: DNA324867, XM\_033912,  
gen.XM\_033912  
Figure 2133: PRO81474  
Figure 2134: DNA324868, XM\_033910,  
gen.XM\_033910  
Figure 2135: DNA324870, NM\_003181,  
gen.NM\_003181  
Figure 2136: PRO81476  
Figure 2137: DNA324871, NM\_002793,  
gen.NM\_002793  
Figure 2138: PRO81477  
Figure 2139: DNA324872, XM\_044866,  
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Figure 2140: DNA324873, XM\_116524,  
gen.XM\_116524  
Figure 2141: DNA324874, XM\_059773,  
gen.XM\_059773  
Figure 2142: DNA324875, XM\_084998,  
gen.XM\_084998  
Figure 2143: PRO81481  
Figure 2144: DNA324876, XM\_058266,  
gen.XM\_058266  
Figure 2145: DNA324877, XM\_042422,  
gen.XM\_042422  
Figure 2146A-B: DNA324878, XM\_054706,  
gen.XM\_054706  
Figure 2147: DNA324879, XM\_166049,  
gen.XM\_166049  
Figure 2148: DNA324880, XM\_042473,  
gen.XM\_042473  
Figure 2149: PRO81486  
Figure 2150: DNA324881, XM\_167046,  
gen.XM\_167046  
Figure 2151: PRO23797  
Figure 2152: DNA324882, XM\_071937,  
gen.XM\_071937  
Figure 2153: PRO81487

Figure 2154: DNA324883, XM\_087991,  
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Figure 2155: DNA324884, NM\_005514,  
gen.NM\_005514  
Figure 2156: PRO81490  
Figure 2157: DNA324885, XM\_166327,  
gen.XM\_166327  
Figure 2158: PRO81491  
Figure 2159: DNA324886, XM\_165692,  
gen.XM\_165692  
Figure 2160: DNA324887, XM\_117449,  
gen.XM\_117449  
Figure 2161: DNA324888, XM\_086428,  
gen.XM\_086428  
Figure 2162: PRO81494  
Figure 2163: DNA324889, NM\_032350,  
gen.NM\_032350  
Figure 2164: PRO81495  
Figure 2165: DNA324890, NM\_013393,  
gen.NM\_013393  
Figure 2166: PRO81496  
Figure 2167: DNA324891, XM\_165860,  
gen.XM\_165860  
Figure 2168: DNA324892, XM\_166541,  
gen.XM\_166541  
Figure 2169: PRO81498  
Figure 2170A-B: DNA324893, XM\_166523,  
gen.XM\_166523  
Figure 2171: PRO81499  
Figure 2172: DNA324894, NM\_016003,  
gen.NM\_016003  
Figure 2173: PRO81500  
Figure 2174: DNA225631, NM\_001101,  
gen.NM\_001101  
Figure 2175: PRO36094  
Figure 2176: DNA274326, NM\_003088,  
gen.NM\_003088  
Figure 2177: PRO62244  
Figure 2178: DNA324895, NM\_006303,  
gen.NM\_006303  
Figure 2179: PRO81501  
Figure 2180: DNA324896, NM\_014413,  
gen.NM\_014413  
Figure 2181: PRO60579  
Figure 2182: DNA247595, NM\_006908,  
gen.NM\_006908  
Figure 2183: PRO45014  
Figure 2184: DNA324897, NM\_006854,  
gen.NM\_006854  
Figure 2185: PRO12468  
Figure 2186: DNA324898, NM\_024067,  
gen.NM\_024067  
Figure 2187: PRO81502  
Figure 2188: DNA324899, NM\_002947,  
gen.NM\_002947  
Figure 2189: PRO81503

Figure 2190: DNA324900, XM.166531,  
gen.XM.166531  
Figure 2191: DNA324901, XM.166540,  
gen.XM.166540  
Figure 2192: PRO81505  
Figure 2193: DNA193955, NM.002489,  
gen.NM.002489  
Figure 2194: PRO23362  
Figure 2195: DNA324902, XM.088264,  
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Figure 2196: PRO81506  
Figure 2197: DNA324903, XM.165841,  
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Figure 2198: DNA324904, XM.166521,  
gen.XM.166521  
Figure 2199: PRO81508  
Figure 2200: DNA324905, XM.166506,  
gen.XM.166506  
Figure 2201: PRO81509  
Figure 2202: DNA324906, XM.166505,  
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Figure 2203: DNA324907, XM.166514,  
gen.XM.166514  
Figure 2204: DNA324908, XM.166515,  
gen.XM.166515  
Figure 2205: DNA324909, XM.166512,  
gen.XM.166512  
Figure 2206: DNA227929, NM.019059,  
gen.NM.019059  
Figure 2207: PRO38392  
Figure 2208A-B: DNA324910, NM.018947,  
gen.NM.018947  
Figure 2209: PRO81514  
Figure 2210: DNA324911, NM.002137,  
gen.NM.002137  
Figure 2211: PRO81515  
Figure 2212: DNA324912, NM.031243,  
gen.NM.031243  
Figure 2213: PRO6373  
Figure 2214: DNA324913, NM.007276,  
gen.NM.007276  
Figure 2215: PRO81516  
Figure 2216: DNA324914, NM.016587,  
gen.NM.016587  
Figure 2217: PRO81517  
Figure 2218: DNA324915, XM.040853,  
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Figure 2219: DNA324916, XM.166509,  
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Figure 2220: DNA324917, XM.166513,  
gen.XM.166513  
Figure 2221: PRO81520  
Figure 2222: DNA324918, XM.166504,  
gen.XM.166504  
Figure 2223: PRO81521  
Figure 2224: DNA324919, XM.166494,

gen.XM.166494  
Figure 2225: DNA324920, XM.107825,  
gen.XM.107825  
Figure 2226A-B: DNA324921, NM.022748,  
gen.NM.022748  
Figure 2227: PRO81523  
Figure 2228: DNA324922, NM.000598,  
gen.NM.000598  
Figure 2229: PRO119  
Figure 2230A-B: DNA324923, XM.166594,  
gen.XM.166594  
Figure 2231: PRO81524  
Figure 2232A-B: DNA275334, NM.030900,  
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Figure 2233: PRO63009  
Figure 2234: DNA324924, NM.031443,  
gen.NM.031443  
Figure 2235: PRO81525  
Figure 2236: DNA324925, NM.012412,  
gen.NM.012412  
Figure 2237: PRO61812  
Figure 2238: DNA324926, NM.021130,  
gen.NM.021130  
Figure 2239: PRO7427  
Figure 2240A-B: DNA324927, XM.165877,  
gen.XM.165877  
Figure 2241: PRO81526  
Figure 2242: DNA227268, NM.019082,  
gen.NM.019082  
Figure 2243: PRO37731  
Figure 2244: DNA324928, XM.015258,  
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Figure 2245: DNA324929, XM.165870,  
gen.XM.165870  
Figure 2246: DNA273865, NM.006230,  
gen.NM.006230  
Figure 2247: PRO61824  
Figure 2248A-B: DNA324930, XM.165882,  
gen.XM.165882  
Figure 2249: DNA324931, XM.165867,  
gen.XM.165867  
Figure 2250: PRO61688  
Figure 2251: DNA324932, NM.014063,  
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Figure 2252: PRO81529  
Figure 2253: DNA324933, XM.165872,  
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Figure 2254: DNA304707, NM.002787,  
gen.NM.002787  
Figure 2255: PRO71133  
Figure 2256: DNA324934, XM.016733,  
gen.XM.016733  
Figure 2257: PRO81531  
Figure 2258: DNA324935, XM.165876,  
gen.XM.165876  
Figure 2259A-B: DNA324936, NM.014800,



gen.NM.014800  
Figure 2260: DNA324937, NM.130442,  
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Figure 2261: PRO81534  
Figure 2262: DNA226416, NM.000385,  
gen.NM.000385  
Figure 2263: PRO36879  
Figure 2264A-B: DNA324938, XM.167339,  
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Figure 2265: DNA287189, NM.002047,  
gen.NM.002047  
Figure 2266: PRO69475  
Figure 2267: DNA324939, XM.170195,  
gen.XM.170195  
Figure 2268: PRO81536  
Figure 2269: DNA324940, XM.168378,  
gen.XM.168378  
Figure 2270: PRO81537  
Figure 2271: DNA324941, XM.168354,  
gen.XM.168354  
Figure 2272: PRO81538  
Figure 2273: DNA324942, XM.167494,  
gen.XM.167494  
Figure 2274: DNA103588, NM.001762,  
gen.NM.001762  
Figure 2275: PRO4912  
Figure 2276: DNA324943, XM.037741,  
gen.XM.037741  
Figure 2277: PRO81540  
Figure 2278: DNA324944, XM.050265,  
gen.XM.050265  
Figure 2279: PRO81541  
Figure 2280: DNA324945, XM.017483,  
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Figure 2281A-B: DNA324946, XM.018359,  
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Figure 2282: DNA324947, XM.059876,  
gen.XM.059876  
Figure 2283: PRO81544  
Figure 2284: DNA324948, NM.032951,  
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Figure 2285: PRO81545  
Figure 2286: DNA324949, NM.032953,  
gen.NM.032953  
Figure 2287: PRO81546  
Figure 2288: DNA324950, NM.022170,  
gen.NM.022170  
Figure 2289: PRO81547  
Figure 2290: DNA324951, NM.031992,  
gen.NM.031992  
Figure 2291: PRO81548  
Figure 2292: DNA324952, XM.004901,  
gen.XM.004901  
Figure 2293: DNA324953, NM.016328,  
gen.NM.016328  
Figure 2294: PRO81550

Figure 2295A-B: DNA324954, NM.032999,  
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Figure 2296: PRO81551  
Figure 2297: DNA324955, XM.088239,  
gen.XM.088239  
Figure 2298: PRO81552  
Figure 2299A-B: DNA324956, XM.167500,  
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Figure 2300A-B: DNA324957, XM.167504,  
gen.XM.167504  
Figure 2301: DNA324958, XM.167498,  
gen.XM.167498  
Figure 2302: DNA324959, XM.168454,  
gen.XM.168454  
Figure 2303: PRO81556  
Figure 2304: DNA324960, NM.031925,  
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Figure 2305: PRO81557  
Figure 2306: DNA324961, NM.005918,  
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Figure 2307: PRO81558  
Figure 2308: DNA304710, NM.001540,  
gen.NM.001540  
Figure 2309: PRO71136  
Figure 2310: DNA324962, XM.168470,  
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Figure 2311: DNA324963, XM.168461,  
gen.XM.168461  
Figure 2312A-B: DNA324964, XM.167502,  
gen.XM.167502  
Figure 2313: DNA324965, XM.017442,  
gen.XM.017442  
Figure 2314: PRO81561  
Figure 2315: DNA324966, XM.168450,  
gen.XM.168450  
Figure 2316: DNA324967, XM.168435,  
gen.XM.168435  
Figure 2317: DNA324968, XM.168464,  
gen.XM.168464  
Figure 2318: DNA324969, XM.170427,  
gen.XM.170427  
Figure 2319A-B: DNA324971, NM.015068,  
gen.NM.015068  
Figure 2320: PRO81566  
Figure 2321A-B: DNA324972, XM.167476,  
gen.XM.167476  
Figure 2322: DNA324973, XM.168181,  
gen.XM.168181  
Figure 2323: DNA324974, XM.168251,  
gen.XM.168251  
Figure 2324: PRO81569  
Figure 2325: DNA324975, XM.167477,  
gen.XM.167477  
Figure 2326: DNA324976, NM.005837,  
gen.NM.005837  
Figure 2327: PRO81571

Figure 2328: DNA324977, XM\_167483, gen.XM\_167483  
 Figure 2329: DNA324978, XM\_167484, gen.XM\_167484  
 Figure 2330: PRO81572  
 Figure 2331: DNA324979, NM\_030935, gen.NM\_030935  
 Figure 2332: PRO81573  
 Figure 2333: DNA324980, NM\_019606, gen.NM\_019606  
 Figure 2334: PRO81574  
 Figure 2335: DNA324981, NM\_024070, gen.NM\_024070  
 Figure 2336: PRO81575  
 Figure 2337: DNA324982, XM\_084241, gen.XM\_084241  
 Figure 2338: DNA324983, NM\_006833, gen.NM\_006833  
 Figure 2339: PRO22897  
 Figure 2340: DNA324984, NM\_032164, gen.NM\_032164  
 Figure 2341: PRO81578  
 Figure 2342: DNA304801, NM\_004889, gen.NM\_004889  
 Figure 2343: PRO71211  
 Figure 2344: DNA324985, NM\_006693, gen.NM\_006693  
 Figure 2345: PRO81579  
 Figure 2346: DNA324986, XM\_165839, gen.XM\_165839  
 Figure 2347: PRO81580  
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 Figure 2350: DNA324987, XM\_165836, gen.XM\_165836  
 Figure 2351A-B: DNA324988, XM\_166482, gen.XM\_166482  
 Figure 2352: DNA324989, XM\_088180, gen.XM\_088180  
 Figure 2353A-B: DNA324990, XM\_166485, gen.XM\_166485  
 Figure 2354: PRO81584  
 Figure 2355: DNA324991, NM\_001673, gen.NM\_001673  
 Figure 2356: PRO81585  
 Figure 2357: DNA324992, NM\_133436, gen.NM\_133436  
 Figure 2358: PRO81586  
 Figure 2359: DNA324993, XM\_168586, gen.XM\_168586  
 Figure 2360: PRO81587  
 Figure 2361: DNA83141, NM\_000602, gen.NM\_000602  
 Figure 2362: PRO2604  
 Figure 2363: DNA324994, NM\_057089,

gen.NM\_057089  
 Figure 2364: PRO81588  
 Figure 2365: DNA324995, NM\_001283, gen.NM\_001283  
 Figure 2366: PRO41882  
 Figure 2367: DNA324996, NM\_003378, gen.NM\_003378  
 Figure 2368: PRO81589  
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 Figure 2371: DNA270711, NM\_006349, gen.NM\_006349  
 Figure 2372: PRO59074  
 Figure 2373: DNA324998, NM\_024653, gen.NM\_024653  
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 Figure 2376: DNA325000, NM\_032958, gen.NM\_032958  
 Figure 2377: PRO81591  
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 Figure 2380: DNA325002, XM\_168572, gen.XM\_168572  
 Figure 2381: DNA325003, XM\_071605, gen.XM\_071605  
 Figure 2382: PRO81594  
 Figure 2383: DNA325004, XM\_033876, gen.XM\_033876  
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 Figure 2386: DNA325006, XM\_088073, gen.XM\_088073  
 Figure 2387: DNA325007, XM\_072430, gen.XM\_072430  
 Figure 2388: PRO81598  
 Figure 2389: DNA325008, XM\_050430, gen.XM\_050430  
 Figure 2390: PRO81599  
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 Figure 2392: PRO81600  
 Figure 2393: DNA226560, NM\_006136, gen.NM\_006136  
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 Figure 2396: DNA325011, NM\_005000, gen.NM\_005000  
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 Figure 2398: DNA325012, NM\_001662, gen.NM\_001662

Figure 2399: PRO39773  
Figure 2400: DNA325013, XM\_011618,  
gen.XM\_011618  
Figure 2401: PRO81602  
Figure 2402: DNA325014, XM\_004627,  
gen.XM\_004627  
Figure 2403: DNA325015, XM\_045401,  
gen.XM\_045401  
Figure 2404: DNA325016, XM\_114602,  
gen.XM\_114602  
Figure 2405: PRO81605  
Figure 2406: DNA325017, XM\_117481,  
gen.XM\_117481  
Figure 2407A-C: DNA325018, XM\_045856,  
gen.XM\_045856  
Figure 2408: PRO81607  
Figure 2409A-B: DNA325019, XM\_088105,  
gen.XM\_088105  
Figure 2410: PRO81608  
Figure 2411: DNA325020, XM\_011548,  
gen.XM\_011548  
Figure 2412: PRO81609  
Figure 2413: DNA325021, XM\_045952,  
gen.XM\_045952  
Figure 2414: DNA325022, XM\_046001,  
gen.XM\_046001  
Figure 2415: PRO81611  
Figure 2416: DNA325023, XM\_088099,  
gen.XM\_088099  
Figure 2417: DNA325024, XM\_040498,  
gen.XM\_040498  
Figure 2418: DNA325025, XM\_088103,  
gen.XM\_088103  
Figure 2419: PRO81614  
Figure 2420: DNA325026, XM\_088122,  
gen.XM\_088122  
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gen.XM\_088119  
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gen.NM\_001628  
Figure 2424: PRO81617  
Figure 2425: DNA325029, NM\_020299,  
gen.NM\_020299  
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Figure 2427: DNA325030, NM\_024033,  
gen.NM\_024033  
Figure 2428: PRO81619  
Figure 2429: DNA325031, XM\_114555,  
gen.XM\_114555  
Figure 2430: DNA325032, XM\_059839,  
gen.XM\_059839  
Figure 2431: PRO81621  
Figure 2432: DNA325033, XM\_095146,  
gen.XM\_095146  
Figure 2433: DNA325034, XM\_016700,

gen.XM\_016700  
Figure 2434: DNA325035, XM\_042781,  
gen.XM\_042781  
Figure 2435: DNA304685, NM\_003143,  
gen.NM\_003143  
Figure 2436: PRO71111  
Figure 2437: DNA325036, NM\_018238,  
gen.NM\_018238  
Figure 2438: PRO81625  
Figure 2439: DNA325037, XM\_035107,  
gen.XM\_035107  
Figure 2440: DNA325038, NM\_003461,  
gen.NM\_003461  
Figure 2441: PRO10194  
Figure 2442: DNA325039, NM\_004911,  
gen.NM\_004911  
Figure 2443: PRO2733  
Figure 2444A-B: DNA325040, XM\_114578,  
gen.XM\_114578  
Figure 2445: PRO81627  
Figure 2446: DNA325041, XM\_088135,  
gen.XM\_088135  
Figure 2447: DNA325042, XM\_098654,  
gen.XM\_098654  
Figure 2448: PRO81629  
Figure 2449: DNA325043, NM\_023942,  
gen.NM\_023942  
Figure 2450: PRO81630  
Figure 2451: DNA325044, NM\_138434,  
gen.NM\_138434  
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Figure 2453: DNA325045, XM\_084238,  
gen.XM\_084238  
Figure 2454A-B: DNA325046, XM\_032216,  
gen.XM\_032216  
Figure 2455A-B: DNA325047, XM\_032121,  
gen.XM\_032121  
Figure 2456: DNA325048, NM\_031434,  
gen.NM\_031434  
Figure 2457: PRO1555  
Figure 2458: DNA226337, NM\_005692,  
gen.NM\_005692  
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Figure 2460: DNA325049, NM\_005614,  
gen.NM\_005614  
Figure 2461: PRO37938  
Figure 2462A-B: DNA325050, NM\_053043,  
gen.NM\_053043  
Figure 2463: PRO81634  
Figure 2464: DNA325051, NM\_022458,  
gen.NM\_022458  
Figure 2465: PRO81635  
Figure 2466: DNA325052, XM\_098669,  
gen.XM\_098669  
Figure 2467: DNA325053, NM\_017760,  
gen.NM\_017760

Figure 2468: PRO81637  
Figure 2469: DNA325054, XM\_036413,  
gen.XM\_036413  
Figure 2470A-B: DNA325055, XM\_032944,  
gen.XM\_032944  
Figure 2471: DNA325056, XM\_117444,  
gen.XM\_117444  
Figure 2472: DNA325057, XM\_117452,  
gen.XM\_117452  
Figure 2473: DNA325058, XM\_070203,  
gen.XM\_070203  
Figure 2474: PRO81641  
Figure 2475: DNA325059, XM\_095371,  
gen.XM\_095371  
Figure 2476: DNA325060, NM\_004084,  
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Figure 2477: PRO2570  
Figure 2478: DNA325061, NM\_005217,  
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Figure 2479: PRO9980  
Figure 2480: DNA325062, XM\_070188,  
gen.XM\_070188  
Figure 2481: PRO81643  
Figure 2482: DNA325063, XM\_035680,  
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Figure 2483: DNA325064, XM\_035662,  
gen.XM\_035662  
Figure 2484: PRO3344  
Figure 2485: DNA325065, XM\_005305,  
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Figure 2486: PRO81645  
Figure 2487: DNA325066, XM\_050293,  
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Figure 2488A-B: DNA325067, XM\_027679,  
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Figure 2489: PRO81647  
Figure 2490A-B: DNA325068, XM\_027651,  
gen.XM\_027651  
Figure 2491: DNA274178, NM\_005775,  
gen.NM\_005775  
Figure 2492: PRO62108  
Figure 2493: DNA325069, XM\_113557,  
gen.XM\_113557  
Figure 2494: PRO81649  
Figure 2495: DNA83022, NM\_001199,  
gen.NM\_001199  
Figure 2496: PRO2042  
Figure 2497: DNA325070, NM\_006128,  
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Figure 2498: PRO81650  
Figure 2499: DNA325071, NM\_006131,  
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Figure 2500: PRO81651  
Figure 2501: DNA325072, NM\_006132,  
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Figure 2502: PRO81652

Figure 2503: DNA325073, NM\_025232,  
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Figure 2504: PRO81653  
Figure 2505: DNA325074, XM\_027440,  
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Figure 2506: DNA225671, NM\_001831,  
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Figure 2507: PRO36134  
Figure 2508: DNA325075, NM\_024567,  
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Figure 2509: PRO81654  
Figure 2510: DNA325076, NM\_018250,  
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Figure 2511: PRO81655  
Figure 2512: DNA227267, NM\_018660,  
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Figure 2513: PRO37730  
Figure 2514A-B: DNA325077, XM\_095545,  
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Figure 2515: DNA325078, XM\_088338,  
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Figure 2516: PRO81657  
Figure 2517: DNA325079, XM\_114617,  
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Figure 2518: PRO81658  
Figure 2519: DNA325080, XM\_088336,  
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Figure 2520: PRO81659  
Figure 2521: DNA325081, XM\_047083,  
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Figure 2522: PRO81660  
Figure 2523: DNA325082, XM\_114618,  
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Figure 2524: PRO81661  
Figure 2525: DNA325083, XM\_050215,  
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Figure 2526: DNA325084, XM\_113531,  
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Figure 2527: DNA325085, NM\_018310,  
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Figure 2528: PRO81664  
Figure 2529: DNA325086, XM\_088294,  
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Figure 2530: DNA325087, XM\_013112,  
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Figure 2531: DNA325088, XM\_059933,  
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Figure 2532: PRO1108  
Figure 2533: DNA325089, XM\_011629,  
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Figure 2534: DNA325090, NM\_000930,  
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Figure 2535: PRO4  
Figure 2536: DNA325091, NM\_000931,  
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Figure 2537: PRO81668

Figure 2538: DNA325092, NM\_033011,  
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Figure 2539: PRO81669  
Figure 2540: DNA325093, XM\_166063,  
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Figure 2541: DNA325094, NM\_025070,  
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Figure 2543A-B: DNA325095, XM\_030268,  
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Figure 2544: DNA325096, XM\_030274,  
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Figure 2545: PRO81673  
Figure 2546: DNA151010, NM\_003350,  
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Figure 2547: PRO12838  
Figure 2548: DNA325097, XM\_113540,  
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Figure 2549: PRO81674  
Figure 2550: DNA325098, NM\_006330,  
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Figure 2551: PRO59230  
Figure 2552: DNA325099, NM\_001023,  
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Figure 2553: PRO58263  
Figure 2554: DNA325100, XM\_095667,  
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Figure 2555: PRO81675  
Figure 2556: DNA325101, XM\_114640,  
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Figure 2557: DNA325102, XM\_057780,  
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Figure 2558: DNA325103, XM\_166064,  
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Figure 2559: DNA325104, XM\_088399,  
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Figure 2560: DNA325105, XM\_088401,  
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Figure 2561: DNA325106, XM\_042658,  
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Figure 2562: DNA325107, XM\_011769,  
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Figure 2563: DNA325108, XM\_044627,  
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Figure 2564: DNA325109, XM\_098761,  
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Figure 2565: DNA226496, NM\_006837,  
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Figure 2566: PRO36959  
Figure 2567: DNA325110, NM\_014294,  
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Figure 2568: PRO23248  
Figure 2569: DNA325111, NM\_000971,  
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Figure 2570: PRO81685  
Figure 2571: DNA325112, XM\_050731,

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Figure 2572: DNA325113, XM\_088325,  
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Figure 2573: PRO81687  
Figure 2574: DNA325114, XM\_088323,  
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Figure 2576: PRO81689  
Figure 2577: DNA325116, XM\_013127,  
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Figure 2578: PRO81690  
Figure 2579: DNA325117, XM\_165514,  
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Figure 2580: PRO81691  
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Figure 2582: DNA325119, XM\_098747,  
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Figure 2583: DNA325120, XM\_050506,  
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Figure 2584: DNA325121, NM\_024613,  
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Figure 2585: PRO81695  
Figure 2586: DNA325122, XM\_011642,  
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Figure 2587: PRO81696  
Figure 2588: DNA325123, NM\_000989,  
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Figure 2589: PRO11265  
Figure 2590: DNA325124, NM\_003406,  
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Figure 2591: PRO71091  
Figure 2592: DNA325125, XM\_011657,  
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Figure 2593: DNA131588, NM\_002568,  
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Figure 2594: PRO7445  
Figure 2595: DNA325126, XM\_018287,  
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Figure 2596: DNA325127, NM\_001568,  
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Figure 2597: PRO81699  
Figure 2598: DNA325128, NM\_003756,  
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Figure 2599: PRO81700  
Figure 2600A-B: DNA272050, NM\_006265,  
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Figure 2602: DNA325129, NM\_052886,  
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Figure 2603: PRO81701  
Figure 2604: DNA325130, XM\_016047,  
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Figure 2605: DNA325131, XM\_005060,  
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Figure 2606: DNA325132, NM\_005005,  
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Figure 2607: PRO81704  
Figure 2608: DNA325133, XM\_037657,  
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Figure 2609: DNA325134, XM\_029567,  
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Figure 2610: PRO81705  
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Figure 2613: DNA325137, XM\_088370,  
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Figure 2614: DNA325138, NM\_016647,  
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Figure 2615: PRO23201  
Figure 2616: DNA325139, NM\_052963,  
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Figure 2617: PRO81708  
Figure 2618: DNA325140, XM\_049247,  
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Figure 2620: DNA325143, NM\_023078,  
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Figure 2621: PRO81711  
Figure 2622: DNA325144, XM\_117487,  
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Figure 2623: DNA325145, XM\_049226,  
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Figure 2624: PRO81714  
Figure 2625: DNA325146, XM\_114613,  
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Figure 2626: DNA325147, XM\_035368,  
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Figure 2627: DNA325148, XM\_113532,  
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Figure 2628: DNA325149, XM\_088321,  
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Figure 2629: DNA325150, XM\_035373,  
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Figure 2630: PRO81719  
Figure 2631: DNA325151, XM\_035370,  
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Figure 2632: PRO81720  
Figure 2633: DNA325152, NM\_000973,  
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Figure 2634: PRO22907  
Figure 2635: DNA325153, NM\_033301,  
gen.NM\_033301  
Figure 2636: PRO22907  
Figure 2637: DNA325154, XM\_049421,  
gen.XM\_049421  
Figure 2638: DNA325155, XM\_034640,  
gen.XM\_034640

Figure 2639: PRO81722  
Figure 2640: DNA325156, XM\_088550,  
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Figure 2641: DNA325157, XM\_088552,  
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Figure 2642: DNA325158, XM\_088553,  
gen.XM\_088553  
Figure 2643: PRO81725  
Figure 2644: DNA325159, XM\_059979,  
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Figure 2645: DNA325160, XM\_167558,  
gen.XM\_167558  
Figure 2646: DNA325161, XM\_039654,  
gen.XM\_039654  
Figure 2647: DNA325162, XM\_060006,  
gen.XM\_060006  
Figure 2648: PRO81729  
Figure 2649: DNA325163, NM\_001122,  
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Figure 2650: PRO81730  
Figure 2651: DNA325164, NM\_001010,  
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Figure 2652: PRO10824  
Figure 2653: DNA325165, NM\_058195,  
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Figure 2654: PRO81731  
Figure 2655: DNA325166, NM\_000077,  
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Figure 2656: PRO36693  
Figure 2657: DNA325167, NM\_058196,  
gen.NM\_058196  
Figure 2658: PRO81732  
Figure 2659: DNA325168, XM\_017931,  
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Figure 2660: DNA271847, NM\_001539,  
gen.NM\_001539  
Figure 2661: PRO60127  
Figure 2662: DNA270991, NM\_004323,  
gen.NM\_004323  
Figure 2663: PRO59321  
Figure 2664: DNA325169, NM\_016410,  
gen.NM\_016410  
Figure 2665: PRO81734  
Figure 2666: DNA325170, XM\_005543,  
gen.XM\_005543  
Figure 2667: PRO38028  
Figure 2668: DNA325171, NM\_001842,  
gen.NM\_001842  
Figure 2669: PRO21481  
Figure 2670: DNA226345, NM\_005866,  
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Figure 2671: PRO36808  
Figure 2672: DNA325172, XM\_088563,  
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Figure 2673: DNA325173, XM\_059998,  
gen.XM\_059998

Figure 2674: PRO59579  
Figure 2675: DNA325174, NM\_013442,  
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Figure 2676: PRO9819  
Figure 2677: DNA325175, XM\_114661,  
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Figure 2678: PRO81736  
Figure 2679: DNA325176, XM\_048479,  
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Figure 2680: DNA290319, NM\_003289,  
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Figure 2681: PRO70595  
Figure 2682A-C: DNA325177, NM\_006289,  
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Figure 2683: PRO81738  
Figure 2684: DNA325178, XM\_048518,  
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Figure 2685: PRO81739  
Figure 2686: DNA325179, XM\_048539,  
gen.XM\_048539  
Figure 2687: PRO81740  
Figure 2688: DNA325180, XM\_114662,  
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Figure 2689: DNA325181, NM\_001833,  
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Figure 2690: PRO81742  
Figure 2691: DNA227491, NM\_007096,  
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Figure 2692: PRO37954  
Figure 2693: DNA254771, NM\_012203,  
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Figure 2694: PRO49869  
Figure 2695: DNA89242, NM\_000700,  
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Figure 2696: PRO2907  
Figure 2697: DNA325182, XM\_041020,  
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Figure 2698: PRO81743  
Figure 2699: DNA325183, XM\_114686,  
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Figure 2700: DNA325184, XM\_088637,  
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Figure 2701: DNA287216, NM\_021154,  
gen.NM\_021154  
Figure 2702: PRO69496  
Figure 2703: DNA288247, NM\_058179,  
gen.NM\_058179  
Figure 2704: PRO70011  
Figure 2705: DNA325185, XM\_071178,  
gen.XM\_071178  
Figure 2706: PRO81746  
Figure 2707: DNA325186, XM\_005490,  
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Figure 2708: DNA325187, NM\_031263,  
gen.NM\_031263  
Figure 2709: PRO81748

Figure 2710: DNA325188, XM\_018006,  
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Figure 2711: DNA325189, XM\_017996,  
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Figure 2712: DNA325190, XM\_016113,  
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Figure 2713: PRO81751  
Figure 2714: DNA272655, NM\_001827,  
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Figure 2715: PRO60781  
Figure 2716A-B: DNA325191, NM\_002161,  
gen.NM\_002161  
Figure 2717: PRO81752  
Figure 2718A-B: DNA325192, NM\_013417,  
gen.NM\_013417  
Figure 2719: PRO81753  
Figure 2720A-B: DNA325193, XM\_046863,  
gen.XM\_046863  
Figure 2721: PRO81754  
Figure 2722: DNA325194, XM\_046836,  
gen.XM\_046836  
Figure 2723: DNA275322, NM\_003837,  
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Figure 2724: PRO63000  
Figure 2725A-B: DNA325195, XM\_098943,  
gen.XM\_098943  
Figure 2726: DNA325196, XM\_016308,  
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Figure 2727: DNA325197, XM\_005525,  
gen.XM\_005525  
Figure 2728: DNA325198, NM\_003389,  
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Figure 2729: PRO81759  
Figure 2730: DNA325199, NM\_033219,  
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Figure 2731: PRO81760  
Figure 2732: DNA325200, NM\_006401,  
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Figure 2733: PRO81761  
Figure 2734: DNA272213, NM\_002486,  
gen.NM\_002486  
Figure 2735: PRO60475  
Figure 2736: DNA325201, NM\_001333,  
gen.NM\_001333  
Figure 2737: PRO81762  
Figure 2738: DNA325202, XM\_116818,  
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Figure 2739: PRO81763  
Figure 2740: DNA254543, NM\_006808,  
gen.NM\_006808  
Figure 2741: PRO49648  
Figure 2742: DNA325203, XM\_070873,  
gen.XM\_070873  
Figure 2743: PRO81764  
Figure 2744: DNA325204, XM\_042788,  
gen.XM\_042788

Figure 2745: PRO81765  
Figure 2746: DNA257309, NM\_032342,  
gen.NM\_032342  
Figure 2747: PRO51901  
Figure 2748: DNA325205, XM\_088569,  
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Figure 2749: PRO81766  
Figure 2750: DNA325206, XM\_088571,  
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Figure 2751: DNA271722, NM\_004697,  
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Figure 2752: PRO60006  
Figure 2753: DNA325207, NM\_017443,  
gen.NM\_017443  
Figure 2754: PRO81768  
Figure 2755A-C: DNA325208, XM\_005348,  
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Figure 2756: DNA325209, XM\_114646,  
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Figure 2757: DNA325210, XM\_038391,  
gen.XM\_038391  
Figure 2758: PRO81771  
Figure 2759A-B: DNA325211, XM\_045296,  
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Figure 2760: DNA325212, XM\_005365,  
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Figure 2761: DNA289530, NM\_004435,  
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Figure 2762: PRO70290  
Figure 2763: DNA287271, NM\_032799,  
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Figure 2764: PRO69542  
Figure 2765: DNA325213, XM\_026987,  
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Figure 2766: DNA325214, XM\_026985,  
gen.XM\_026985  
Figure 2767: DNA225630, NM\_016174,  
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Figure 2768: PRO36093  
Figure 2769: DNA325215, XM\_026968,  
gen.XM\_026968  
Figure 2770: PRO81775  
Figure 2771: DNA325216, XM\_026951,  
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Figure 2772: DNA325217, NM\_025072,  
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Figure 2773: PRO33818  
Figure 2774: DNA325218, XM\_033424,  
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Figure 2775: DNA325219, NM\_004957,  
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Figure 2776: PRO81778  
Figure 2777: DNA325220, XM\_033457,  
gen.XM\_033457  
Figure 2778A-B: DNA325221, XM\_033460,  
gen.XM\_033460

Figure 2779: PRO81780  
Figure 2780: DNA325222, NM\_000976,  
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Figure 2781: PRO62236  
Figure 2782: DNA218841, NM\_012098,  
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Figure 2783: PRO34473  
Figure 2784A-B: DNA325223, XM\_052725,  
gen.XM\_052725  
Figure 2785: PRO81781  
Figure 2786: DNA325224, XM\_011752,  
gen.XM\_011752  
Figure 2787: DNA325225, XM\_026944,  
gen.XM\_026944  
Figure 2788: PRO81783  
Figure 2789: DNA325226, XM\_116806,  
gen.XM\_116806  
Figure 2790A-B: DNA325227, NM\_005347,  
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Figure 2791: PRO81785  
Figure 2792: DNA325228, NM\_005833,  
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Figure 2793: PRO81786  
Figure 2794: DNA325229, NM\_007209,  
gen.NM\_007209  
Figure 2795: PRO61897  
Figure 2796: DNA88350, NM\_000177,  
gen.NM\_000177  
Figure 2797: PRO2758  
Figure 2798A-B: DNA325230, XM\_011749,  
gen.XM\_011749  
Figure 2799: DNA325231, XM\_114679,  
gen.XM\_114679  
Figure 2800: DNA325232, XM\_087041,  
gen.XM\_087041  
Figure 2801: DNA325233, XM\_114678,  
gen.XM\_114678  
Figure 2802: DNA325234, XM\_114677,  
gen.XM\_114677  
Figure 2803: DNA325235, XM\_087038,  
gen.XM\_087038  
Figure 2804: DNA325236, XM\_059637,  
gen.XM\_059637  
Figure 2805: PRO81792  
Figure 2806: DNA325237, NM\_000368,  
gen.NM\_000368  
Figure 2807: PRO60115  
Figure 2808: DNA325238, XM\_033385,  
gen.XM\_033385  
Figure 2809A-B: DNA325239, XM\_033380,  
gen.XM\_033380  
Figure 2810: PRO81794  
Figure 2811: DNA325240, XM\_033362,  
gen.XM\_033362  
Figure 2812: PRO81795  
Figure 2813: DNA325241, XM\_059986,



gen.XM\_059986  
 Figure 2814: PRO81796  
 Figure 2815A-B: DNA325242, XM\_033361,  
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 Figure 2816: PRO81797  
 Figure 2817A-B: DNA325243, XM\_033360,  
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 Figure 2818: DNA325244, XM\_033359,  
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 Figure 2819A-B: DNA325245, XM\_033355,  
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 Figure 2820: DNA325246, NM\_014285,  
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 Figure 2822: DNA325247, NM\_054012,  
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 Figure 2823: PRO81801  
 Figure 2824: DNA325248, XM\_035103,  
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 Figure 2825: DNA325249, XM\_035109,  
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 Figure 2826: DNA325250, NM\_000972,  
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 Figure 2827: PRO81804  
 Figure 2828: DNA325251, NM\_033161,  
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 Figure 2829: PRO81805  
 Figure 2830: DNA325252, NM\_000787,  
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 Figure 2831: PRO81806  
 Figure 2832A-B: DNA325253, XM\_011778,  
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 Figure 2833: DNA325254, XM\_088426,  
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 Figure 2834: DNA325255, NM\_002003,  
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 Figure 2835: PRO1910  
 Figure 2836: DNA325256, NM\_058199,  
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 Figure 2837: PRO81809  
 Figure 2838: DNA325257, XM\_059945,  
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 Figure 2839: DNA325258, XM\_088422,  
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 Figure 2840: PRO81811  
 Figure 2841: DNA325259, XM\_029168,  
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 Figure 2842: PRO81812  
 Figure 2843: DNA325260, XM\_098913,  
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 Figure 2844: PRO81813  
 Figure 2845: DNA325261, XM\_114669,  
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 Figure 2846: DNA325262, XM\_113564,  
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 Figure 2847A-B: DNA325263, XM\_088459,

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 Figure 2848: PRO81815  
 Figure 2849: DNA325264, XM\_054752,  
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 Figure 2850: PRO81816  
 Figure 2851: DNA325265, XM\_084270,  
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 Figure 2852: DNA325266, XM\_054763,  
 gen.XM\_054763  
 Figure 2853: PRO81817  
 Figure 2854: DNA325267, XM\_114655,  
 gen.XM\_114655  
 Figure 2855: DNA325268, XM\_038030,  
 gen.XM\_038030  
 Figure 2856: PRO59351  
 Figure 2857: DNA325269, XM\_072526,  
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 Figure 2858: PRO81819  
 Figure 2859: DNA325270, XM\_059961,  
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 Figure 2860: DNA325271, NM\_032928,  
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 Figure 2861: PRO81821  
 Figure 2862: DNA325272, NM\_014172,  
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 Figure 2863: PRO81822  
 Figure 2864: DNA325273, XM\_038049,  
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 Figure 2865: PRO62069  
 Figure 2866: DNA325274, XM\_038063,  
 gen.XM\_038063  
 Figure 2867: PRO81823  
 Figure 2868: DNA325275, NM\_000954,  
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 Figure 2869: PRO81824  
 Figure 2870: DNA325276, XM\_088461,  
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 Figure 2871: DNA325277, XM\_059966,  
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 Figure 2872: PRO81826  
 Figure 2873: DNA325278, XM\_114649,  
 gen.XM\_114649  
 Figure 2874: DNA325279, XM\_117519,  
 gen.XM\_117519  
 Figure 2875: DNA325280, XM\_053206,  
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 Figure 2876: DNA325281, XM\_040272,  
 gen.XM\_040272  
 Figure 2877: PRO58939  
 Figure 2878: DNA325282, XM\_005724,  
 gen.XM\_005724  
 Figure 2879: DNA325283, XM\_040267,  
 gen.XM\_040267  
 Figure 2880: PRO81831  
 Figure 2881: DNA325284, XM\_048859,  
 gen.XM\_048859

Figure 2882: PRO62617  
Figure 2883: DNA325285, NM\_003739,  
gen.NM\_003739  
Figure 2884: PRO81832  
Figure 2885: DNA325286, XM\_060976,  
gen.XM\_060976  
Figure 2886: PRO81833  
Figure 2887: DNA325287, XM\_167626,  
gen.XM\_167626  
Figure 2888: PRO81834  
Figure 2889: DNA325288, XM\_165555,  
gen.XM\_165555  
Figure 2890: PRO81835  
Figure 2891: DNA325289, NM\_001494,  
gen.NM\_001494  
Figure 2892: PRO81836  
Figure 2893: DNA325290, NM\_032905,  
gen.NM\_032905  
Figure 2894: PRO81837  
Figure 2895: DNA325291, NM\_005174,  
gen.NM\_005174  
Figure 2896: PRO81838  
Figure 2897: DNA325292, XM\_165557,  
gen.XM\_165557  
Figure 2898: DNA325293, XM\_167374,  
gen.XM\_167374  
Figure 2899: DNA273759, NM\_006023,  
gen.NM\_006023  
Figure 2900: PRO61721  
Figure 2901: DNA325294, XM\_167411,  
gen.XM\_167411  
Figure 2902: DNA325295, NM\_031453,  
gen.NM\_031453  
Figure 2903: PRO81841  
Figure 2904: DNA325296, XM\_167414,  
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Figure 2905: PRO12851  
Figure 2906: DNA325297, XM\_166717,  
gen.XM\_166717  
Figure 2907: PRO81842  
Figure 2908: DNA325298, XM\_005100,  
gen.XM\_005100  
Figure 2909: DNA325299, XM\_038536,  
gen.XM\_038536  
Figure 2910A-B: DNA325300, XM\_084420,  
gen.XM\_084420  
Figure 2911: DNA325301, XM\_084429,  
gen.XM\_084429  
Figure 2912: PRO81846  
Figure 2913A-C: DNA325302, XM\_165551,  
gen.XM\_165551  
Figure 2914: DNA325303, XM\_059720,  
gen.XM\_059720  
Figure 2915: PRO81848  
Figure 2916A-B: DNA325304, NM\_019619,  
gen.NM\_019619

Figure 2917: PRO81849  
Figure 2918: DNA325305, XM\_166665,  
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Figure 2919A-B: DNA325306, NM\_002211,  
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Figure 2920: PRO81851  
Figure 2921A-B: DNA325307, XM\_165567,  
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Figure 2922: DNA325308, XM\_166157,  
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Figure 2923: DNA325309, NM\_032023,  
gen.NM\_032023  
Figure 2924: PRO52537  
Figure 2925: DNA325310, XM\_165560,  
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Figure 2926: DNA325311, XM\_165563,  
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Figure 2927: DNA325312, XM\_113615,  
gen.XM\_113615  
Figure 2928: PRO81855  
Figure 2929: DNA325313, XM\_165890,  
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Figure 2930: DNA325314, XM\_061126,  
gen.XM\_061126  
Figure 2931: DNA325315, XM\_061125,  
gen.XM\_061125  
Figure 2932: PRO81858  
Figure 2933: DNA325316, XM\_054474,  
gen.XM\_054474  
Figure 2934: DNA325317, XM\_165888,  
gen.XM\_165888  
Figure 2935: DNA325318, XM\_054475,  
gen.XM\_054475  
Figure 2936: PRO81861  
Figure 2937: DNA325319, XM\_015652,  
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Figure 2938: PRO81862  
Figure 2939: DNA325320, XM\_036593,  
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Figure 2940: PRO81863  
Figure 2941: DNA325321, XM\_165891,  
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Figure 2942: DNA325322, XM\_084450,  
gen.XM\_084450  
Figure 2943: PRO81865  
Figure 2944: DNA325323, XM\_084385,  
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Figure 2945: DNA325324, NM\_021226,  
gen.NM\_021226  
Figure 2946: PRO81867  
Figure 2947: DNA193957, NM\_003055,  
gen.NM\_003055  
Figure 2948: PRO23364  
Figure 2949: DNA325325, NM\_032997,  
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Figure 2950: PRO81868

Figure 2951: DNA287642, NM\_018464,  
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Figure 2952: PRO9902  
Figure 2953: DNA325326, XM\_084451,  
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Figure 2954: PRO81869  
Figure 2955: DNA325327, NM\_012207,  
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Figure 2956: PRO81870  
Figure 2957: DNA325328, NM\_024045,  
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Figure 2958: PRO81871  
Figure 2959: DNA325329, NM\_004728,  
gen.NM\_004728  
Figure 2960: PRO81872  
Figure 2961: DNA88562, NM\_002727,  
gen.NM\_002727  
Figure 2962: PRO2842  
Figure 2963: DNA325330, XM\_167395,  
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Figure 2964: DNA227172, NM\_021129,  
gen.NM\_021129  
Figure 2965: PRO37635  
Figure 2966A-B: DNA325331, XM\_166125,  
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Figure 2967: PRO81874  
Figure 2968: DNA325332, XM\_044354,  
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Figure 2969: PRO81875  
Figure 2970: DNA325333, XM\_032520,  
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Figure 2971: DNA325334, NM\_019058,  
gen.NM\_019058  
Figure 2972: PRO81877  
Figure 2973: DNA325335, XM\_045140,  
gen.XM\_045140  
Figure 2974: PRO2875  
Figure 2975: DNA325336, XM\_116863,  
gen.XM\_116863  
Figure 2976: DNA325337, XM\_032476,  
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Figure 2977: DNA325338, XM\_114894,  
gen.XM\_114894  
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gen.NM\_033022  
Figure 2979: PRO81881  
Figure 2980: DNA325340, NM\_001026,  
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Figure 2981: PRO11139  
Figure 2982: DNA103421, NM\_003375,  
gen.NM\_003375  
Figure 2983: PRO4749  
Figure 2984A-B: DNA325341, XM\_166093,  
gen.XM\_166093  
Figure 2985: PRO81882  
Figure 2986: DNA304459, NM\_005729,

gen.NM\_005729  
Figure 2987: PRO37073  
Figure 2988: DNA325342, XM\_166629,  
gen.XM\_166629  
Figure 2989: PRO81883  
Figure 2990: DNA103506, NM\_001157,  
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Figure 2991: PRO4833  
Figure 2992: DNA325343, XM\_016093,  
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Figure 2993: PRO81884  
Figure 2994: DNA325344, XM\_084467,  
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Figure 2995: PRO81885  
Figure 2996: DNA304488, NM\_032333,  
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Figure 2997: PRO71057  
Figure 2998: DNA325345, XM\_043589,  
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Figure 2999: DNA325346, XM\_043605,  
gen.XM\_043605  
Figure 3000: DNA325347, XM\_087480,  
gen.XM\_087480  
Figure 3001: PRO81887  
Figure 3002: DNA325348, NM\_002921,  
gen.NM\_002921  
Figure 3003: PRO81888  
Figure 3004: DNA226217, NM\_005271,  
gen.NM\_005271  
Figure 3005: PRO36680  
Figure 3006: DNA325349, XM\_089551,  
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Figure 3007: PRO81889  
Figure 3008: DNA287237, NM\_001613,  
gen.NM\_001613  
Figure 3009: PRO39648  
Figure 3010: DNA325350, XM\_084477,  
gen.XM\_084477  
Figure 3011: PRO69523  
Figure 3012: DNA325351, XM\_084480,  
gen.XM\_084480  
Figure 3013A-B: DNA325352, NM\_013451,  
gen.NM\_013451  
Figure 3014: PRO12813  
Figure 3015: DNA325353, XM\_018167,  
gen.XM\_018167  
Figure 3016: DNA325354, XM\_084372,  
gen.XM\_084372  
Figure 3017: DNA325355, NM\_020992,  
gen.NM\_020992  
Figure 3018: PRO81893  
Figure 3019: DNA325356, XM\_089514,  
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Figure 3020A-B: DNA325357, XM\_058343,  
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Figure 3021: PRO81895

Figure 3022: DNA325358, XM\_058602,  
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Figure 3023: PRO81896  
Figure 3024A-B: DNA325359, NM\_015179,  
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Figure 3025: PRO81897  
Figure 3026: DNA325360, XM\_083842,  
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Figure 3027: PRO69473  
Figure 3028: DNA325361, XM\_084413,  
gen.XM\_084413  
Figure 3029: DNA325362, NM\_022362,  
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Figure 3030: PRO81899  
Figure 3031: DNA325363, NM\_032112,  
gen.NM\_032112  
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Figure 3033: DNA325364, NM\_021830,  
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Figure 3034: PRO81901  
Figure 3035A-B: DNA325365, XM\_046743,  
gen.XM\_046743  
Figure 3036: PRO81902  
Figure 3037: DNA325366, NM\_013274,  
gen.NM\_013274  
Figure 3038: PRO81903  
Figure 3039: DNA325367, NM\_022039,  
gen.NM\_022039  
Figure 3040: PRO81904  
Figure 3041A-B: DNA325368, XM\_031866,  
gen.XM\_031866  
Figure 3042A-B: DNA325369, NM\_015062,  
gen.NM\_015062  
Figure 3043: PRO81905  
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Figure 3047: DNA325372, NM\_024040,  
gen.NM\_024040  
Figure 3048: PRO81908  
Figure 3049: DNA325373, XM\_031949,  
gen.XM\_031949  
Figure 3050: PRO4900  
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gen.NM\_016169  
Figure 3052: PRO34073  
Figure 3053: DNA325374, XM\_005698,  
gen.XM\_005698  
Figure 3054: PRO81909  
Figure 3055: DNA325375, NM\_006523,  
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Figure 3056: PRO59043  
Figure 3057: DNA325376, XM\_018279,  
gen.XM\_018279

Figure 3058A-B: DNA325377, XM\_005938,  
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Figure 3059A-B: DNA325378, XM\_031992,  
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Figure 3060: PRO81912  
Figure 3061: DNA325379, NM\_032747,  
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Figure 3062: PRO81913  
Figure 3063: DNA325380, NM\_005004,  
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Figure 3066: DNA273521, NM\_002079,  
gen.NM\_002079  
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Figure 3068A-B: DNA325382, NM\_032211,  
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Figure 3069: PRO81916  
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Figure 3071: PRO81917  
Figure 3072: DNA325384, XM\_084632,  
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Figure 3073: DNA325385, XM\_084359,  
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Figure 3074A-D: DNA325386, XM\_045667,  
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Figure 3075: DNA325387, XM\_109162,  
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Figure 3076: DNA227509, NM\_000274,  
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Figure 3077: PRO37972  
Figure 3078: DNA325388, XM\_058361,  
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Figure 3079: PRO81922  
Figure 3080: DNA325389, XM\_084505,  
gen.XM\_084505  
Figure 3081: PRO81923  
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Figure 3085: PRO81925  
Figure 3086: DNA325392, XM\_055573,  
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Figure 3087: PRO60991  
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Figure 3089: DNA325394, NM\_007190,  
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Figure 3091: DNA325395, NM\_000982,  
gen.NM\_000982  
Figure 3092: PRO81927

Figure 3093: DNA269952, NM\_004725,  
gen.NM\_004725  
Figure 3094: PRO58348  
Figure 3095: DNA325396, NM\_024942,  
gen.NM\_024942  
Figure 3096: PRO81928  
Figure 3097: DNA325397, NM\_016567,  
gen.NM\_016567  
Figure 3098: PRO81929  
Figure 3099: DNA325398, NM\_004092,  
gen.NM\_004092  
Figure 3100: PRO81930  
Figure 3101: DNA269431, NM\_006659,  
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Figure 3102: PRO57854  
Figure 3103: DNA325399, XM\_005675,  
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Figure 3104: DNA325400, XM\_114862,  
gen.XM\_114862  
Figure 3105: PRO81932  
Figure 3106: DNA325401, XM\_088009,  
gen.XM\_088009  
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gen.NM\_016526  
Figure 3108: PRO81934  
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gen.NM\_021932  
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Figure 3111: DNA325403, XM\_043220,  
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Figure 3112: PRO81935  
Figure 3113: DNA255078, NM\_006435,  
gen.NM\_006435  
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Figure 3115: DNA325404, NM\_002339,  
gen.NM\_002339  
Figure 3116: PRO81936  
Figure 3117: DNA325405, XM\_028192,  
gen.XM\_028192  
Figure 3118: PRO81937  
Figure 3119: DNA325406, XM\_096544,  
gen.XM\_096544  
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gen.NM\_000612  
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gen.XM\_084742  
Figure 3123: PRO81939  
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gen.XM\_084739  
Figure 3125: DNA325410, XM\_058505,  
gen.XM\_058505  
Figure 3126: PRO81941  
Figure 3127: DNA325411, XM\_006139,  
gen.XM\_006139  
Figure 3128: PRO81942

Figure 3129: DNA325412, XM\_044932,  
gen.XM\_044932  
Figure 3130: PRO81943  
Figure 3131A-B: DNA325413, XM\_044957,  
gen.XM\_044957  
Figure 3132: PRO81944  
Figure 3133: DNA325414, NM\_001909,  
gen.NM\_001909  
Figure 3134: PRO292  
Figure 3135: DNA325415, XM\_006475,  
gen.XM\_006475  
Figure 3136: DNA325416, XM\_006483,  
gen.XM\_006483  
Figure 3137: DNA325417, NM\_001751,  
gen.NM\_001751  
Figure 3138: PRO69635  
Figure 3139: DNA325418, XM\_114981,  
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gen.XM\_083852  
Figure 3142: DNA325420, NM\_000559,  
gen.NM\_000559  
Figure 3143: PRO81946  
Figure 3144: DNA325421, NM\_000184,  
gen.NM\_000184  
Figure 3145: PRO81947  
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gen.NM\_005330  
Figure 3147: PRO81948  
Figure 3148: DNA325423, XM\_015243,  
gen.XM\_015243  
Figure 3149: DNA325424, NM\_015324,  
gen.NM\_015324  
Figure 3150: PRO81950  
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gen.XM\_006424  
Figure 3152: DNA325426, XM\_113238,  
gen.XM\_113238  
Figure 3153A-C: DNA325427, XM\_052786,  
gen.XM\_052786  
Figure 3154: PRO81953  
Figure 3155: DNA325428, NM\_000990,  
gen.NM\_000990  
Figure 3156: PRO25985  
Figure 3157A-B: DNA325429, XM\_045750,  
gen.XM\_045750  
Figure 3158: PRO81954  
Figure 3159: DNA325430, XM\_058414,  
gen.XM\_058414  
Figure 3160: PRO81955  
Figure 3161A-B: DNA325431, XM\_049197,  
gen.XM\_049197  
Figure 3162: PRO81956  
Figure 3163A-B: DNA325432, NM\_001418,  
gen.NM\_001418

Figure 3164: PRO81957  
Figure 3165: DNA325433, XM\_096520,  
gen.XM\_096520  
Figure 3166: PRO81958  
Figure 3167: DNA325434, XM\_006212,  
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Figure 3168: PRO81959  
Figure 3169: DNA325435, XM\_084527,  
gen.XM\_084527  
Figure 3170: DNA325436, XM\_016139,  
gen.XM\_016139  
Figure 3171: DNA325437, NM\_001017,  
gen.NM\_001017  
Figure 3172: PRO11262  
Figure 3173: DNA325438, NM\_014267,  
gen.NM\_014267  
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gen.NM\_005566  
Figure 3176: PRO3632  
Figure 3177: DNA325439, XM\_115081,  
gen.XM\_115081  
Figure 3178: DNA325440, XM\_036339,  
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Figure 3179: PRO81964  
Figure 3180: DNA325441, XM\_084514,  
gen.XM\_084514  
Figure 3181: PRO81965  
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Figure 3183: DNA325443, XM\_084515,  
gen.XM\_084515  
Figure 3184: DNA325444, XM\_084517,  
gen.XM\_084517  
Figure 3185: DNA325445, XM\_034431,  
gen.XM\_034431  
Figure 3186: PRO11691  
Figure 3187: DNA325446, XM\_030326,  
gen.XM\_030326  
Figure 3188: DNA325447, NM\_057174,  
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Figure 3189: PRO81970  
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Figure 3191: PRO81971  
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gen.XM\_167437  
Figure 3193: DNA325450, XM\_054856,  
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Figure 3194: DNA325451, XM\_004330,  
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Figure 3195: DNA325452, XM\_084681,  
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Figure 3197: DNA325454, NM\_003646,

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Figure 3198: PRO81977  
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Figure 3200: PRO81978  
Figure 3201: DNA325456, XM\_006170,  
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Figure 3202: DNA325457, XM\_037173,  
gen.XM\_037173  
Figure 3203: PRO81980  
Figure 3204: DNA150974, NM\_005693,  
gen.NM\_005693  
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gen.NM\_001610  
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gen.NM\_000107  
Figure 3209: PRO58523  
Figure 3210: DNA325458, NM\_016223,  
gen.NM\_016223  
Figure 3211: PRO81981  
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gen.XM\_037147  
Figure 3213: PRO81982  
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gen.XM\_015705  
Figure 3215: DNA272728, NM\_003146,  
gen.NM\_003146  
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gen.XM\_165611  
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gen.NM\_024098  
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gen.NM\_014502  
Figure 3221: PRO37551  
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gen.XM\_165610  
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gen.XM\_165612  
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gen.XM\_166234  
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gen.NM\_015533  
Figure 3226: PRO81988  
Figure 3227: DNA325466, XM\_166232,  
gen.XM\_166232  
Figure 3228A-B: DNA325467, XM\_167748,  
gen.XM\_167748  
Figure 3229: PRO81990  
Figure 3230: DNA325468, NM\_004739,  
gen.NM\_004739  
Figure 3231: PRO81991  
Figure 3232: DNA325469, NM\_014610,

gen.NM.014610  
 Figure 3233: PRO81992  
 Figure 3234: DNA325470, XM.167747,  
 gen.XM.167747  
 Figure 3235: PRO81993  
 Figure 3236: DNA287254, NM.024099,  
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 gen.NM.015853  
 Figure 3239: PRO81994  
 Figure 3240: DNA325472, NM.032667,  
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 Figure 3241: PRO81995  
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 Figure 3243: PRO81996  
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 gen.NM.002411  
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 gen.NM.032989  
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 Figure 3261: DNA325484, NM.031472,  
 gen.NM.031472  
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 gen.XM.037808  
 Figure 3264: DNA325486, NM.004074,  
 gen.NM.004074  
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 gen.NM.017670  
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Figure 3268: DNA325488, XM.113223,  
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 Figure 3269: DNA325489, XM.045642,  
 gen.XM.045642  
 Figure 3270: DNA325490, XM.006533,  
 gen.XM.006533  
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 gen.XM.045613  
 Figure 3272: PRO59721  
 Figure 3273A-B: DNA325492, XM.045612,  
 gen.XM.045612  
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 Figure 3275: DNA325493, XM.113224,  
 gen.XM.113224  
 Figure 3276: DNA325494, XM.045499,  
 gen.XM.045499  
 Figure 3277: PRO82011  
 Figure 3278: DNA325495, XM.045525,  
 gen.XM.045525  
 Figure 3279: DNA325496, NM.013265,  
 gen.NM.013265  
 Figure 3280: PRO82013  
 Figure 3281: DNA325497, XM.006529,  
 gen.XM.006529  
 Figure 3282: PRO60008  
 Figure 3283: DNA325498, XM.053787,  
 gen.XM.053787  
 Figure 3284: DNA269803, NM.001667,  
 gen.NM.001667  
 Figure 3285: PRO58207  
 Figure 3286: DNA325499, XM.115031,  
 gen.XM.115031  
 Figure 3287: DNA325500, XM.084702,  
 gen.XM.084702  
 Figure 3288: DNA325501, XM.053796,  
 gen.XM.053796  
 Figure 3289: DNA325502, NM.002689,  
 gen.NM.002689  
 Figure 3290: PRO82018  
 Figure 3291A-D: DNA325503, XM.167804,  
 gen.XM.167804  
 Figure 3292: PRO82019  
 Figure 3293: DNA325504, XM.166235,  
 gen.XM.166235  
 Figure 3294: DNA325505, XM.166236,  
 gen.XM.166236  
 Figure 3295: DNA270721, NM.006842,  
 gen.NM.006842  
 Figure 3296: PRO59084  
 Figure 3297: DNA189687, NM.000852,  
 gen.NM.000852  
 Figure 3298: PRO25845  
 Figure 3299: DNA325506, NM.007103,  
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 Figure 3300: PRO58606  
 Figure 3301: DNA325507, NM.005851,

gen.NM\_005851  
Figure 3302: PRO69461  
Figure 3303A-B: DNA325508, XM\_165598,  
gen.XM\_165598  
Figure 3304: DNA325509, NM\_006019,  
gen.NM\_006019  
Figure 3305: PRO82023  
Figure 3306: DNA325510, NM\_006053,  
gen.NM\_006053  
Figure 3307: PRO24831  
Figure 3308: DNA325511, XM\_166196,  
gen.XM\_166196  
Figure 3309: PRO82024  
Figure 3310: DNA325512, XM\_165600,  
gen.XM\_165600  
Figure 3311A-B: DNA325513, NM\_053056,  
gen.NM\_053056  
Figure 3312: PRO4870  
Figure 3313: DNA103474, NM\_003824,  
gen.NM\_003824  
Figure 3314: PRO4801  
Figure 3315: DNA325514, XM\_096486,  
gen.XM\_096486  
Figure 3316A-B: DNA325515, NM\_003626,  
gen.NM\_003626  
Figure 3317: PRO82027  
Figure 3318A-B: DNA325516, XM\_167853,  
gen.XM\_167853  
Figure 3319: PRO82028  
Figure 3320: DNA325517, NM\_014042,  
gen.NM\_014042  
Figure 3321: PRO82029  
Figure 3322A-B: DNA325518, NM\_001567,  
gen.NM\_001567  
Figure 3323: PRO61238  
Figure 3324: DNA325519, XM\_167433,  
gen.XM\_167433  
Figure 3325: DNA325520, XM\_165616,  
gen.XM\_165616  
Figure 3326: DNA325521, NM\_032871,  
gen.NM\_032871  
Figure 3327: PRO57307  
Figure 3328: DNA325522, XM\_165631,  
gen.XM\_165631  
Figure 3329: DNA254186, NM\_014752,  
gen.NM\_014752  
Figure 3330: PRO49298  
Figure 3331: DNA325523, NM\_001005,  
gen.NM\_001005  
Figure 3332: PRO82032  
Figure 3333: DNA88176, NM\_001235,  
gen.NM\_001235  
Figure 3334: PRO2685  
Figure 3335A-B: DNA325524, XM\_165627,  
gen.XM\_165627  
Figure 3336: DNA325525, XM\_166253,

gen.XM\_166253  
Figure 3337: DNA325526, NM\_001293,  
gen.NM\_001293  
Figure 3338: PRO82034  
Figure 3339: DNA325527, XM\_042852,  
gen.XM\_042852  
Figure 3340: PRO82035  
Figure 3341: DNA325528, XM\_165628,  
gen.XM\_165628  
Figure 3342A-B: DNA325529, NM\_080491,  
gen.NM\_080491  
Figure 3343: PRO82037  
Figure 3344A-B: DNA325530, NM\_012296,  
gen.NM\_012296  
Figure 3345: PRO60311  
Figure 3346: DNA325531, NM\_032379,  
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Figure 3348: DNA325532, NM\_007173,  
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Figure 3349: DNA325533, XM\_166239,  
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Figure 3350: DNA325534, XM\_084610,  
gen.XM\_084610  
Figure 3351: PRO82040  
Figure 3352: DNA325535, XM\_058450,  
gen.XM\_058450  
Figure 3353: DNA325536, XM\_084601,  
gen.XM\_084601  
Figure 3354: PRO82042  
Figure 3355A-B: DNA325537, XM\_006464,  
gen.XM\_006464  
Figure 3356: PRO82043  
Figure 3357: DNA325538, XM\_084570,  
gen.XM\_084570  
Figure 3358: DNA325539, XM\_051435,  
gen.XM\_051435  
Figure 3359: DNA325540, NM\_001467,  
gen.NM\_001467  
Figure 3360: PRO82045  
Figure 3361: DNA325541, NM\_001028,  
gen.NM\_001028  
Figure 3362: PRO82046  
Figure 3363: DNA325542, XM\_113230,  
gen.XM\_113230  
Figure 3364: DNA325543, XM\_115062,  
gen.XM\_115062  
Figure 3365: DNA325544, XM\_115063,  
gen.XM\_115063  
Figure 3366: DNA325545, XM\_113229,  
gen.XM\_113229  
Figure 3367A-B: DNA325546, XM\_051489,  
gen.XM\_051489  
Figure 3368: PRO82050  
Figure 3369: DNA325547, NM\_022003,  
gen.NM\_022003



Figure 3370: PRO82051  
Figure 3371: DNA325548, XM\_006432,  
gen.XM\_006432  
Figure 3372: PRO82052  
Figure 3373: DNA325549, XM\_051716,  
gen.XM\_051716  
Figure 3374: DNA325550, NM\_025164,  
gen.NM\_025164  
Figure 3375: PRO82054  
Figure 3376: DNA225752, NM\_000039,  
gen.NM\_000039  
Figure 3377: PRO36215  
Figure 3378: DNA325551, XM\_052113,  
gen.XM\_052113  
Figure 3379: PRO82055  
Figure 3380: DNA271324, NM\_006169,  
gen.NM\_006169  
Figure 3381: PRO59629  
Figure 3382: DNA325552, XM\_084658,  
gen.XM\_084658  
Figure 3383: PRO82056  
Figure 3384: DNA325553, NM\_000795,  
gen.NM\_000795  
Figure 3385: PRO12448  
Figure 3386: DNA325554, NM\_017868,  
gen.NM\_017868  
Figure 3387: PRO82057  
Figure 3388: DNA325555, XM\_084654,  
gen.XM\_084654  
Figure 3389: PRO82058  
Figure 3390: DNA272413, NM\_003002,  
gen.NM\_003002  
Figure 3391: PRO60666  
Figure 3392: DNA271843, NM\_004398,  
gen.NM\_004398  
Figure 3393: PRO60123  
Figure 3394: DNA325556, XM\_017369,  
gen.XM\_017369  
Figure 3395: DNA325557, NM\_032299,  
gen.NM\_032299  
Figure 3396: PRO82060  
Figure 3397: DNA325558, XM\_055369,  
gen.XM\_055369  
Figure 3398: DNA325559, XM\_051430,  
gen.XM\_051430  
Figure 3399: DNA325560, XM\_006467,  
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Figure 3400: DNA325561, XM\_113226,  
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Figure 3401: DNA325562, XM\_165592,  
gen.XM\_165592  
Figure 3402: PRO82064  
Figure 3403: DNA325563, XM\_166181,  
gen.XM\_166181  
Figure 3404: DNA325564, XM\_052862,  
gen.XM\_052862

Figure 3405: PRO82066  
Figure 3406: DNA325565, XM\_166177,  
gen.XM\_166177  
Figure 3407: DNA325566, XM\_165571,  
gen.XM\_165571  
Figure 3408: PRO82068  
Figure 3409: DNA325567, XM\_166174,  
gen.XM\_166174  
Figure 3410: PRO82069  
Figure 3411: DNA325568, NM\_001274,  
gen.NM\_001274  
Figure 3412: PRO12187  
Figure 3413: DNA325569, XM\_165586,  
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Figure 3414: DNA325570, XM\_165584,  
gen.XM\_165584  
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gen.NM\_032873  
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gen.XM\_167780  
Figure 3418: DNA325572, XM\_166743,  
gen.XM\_166743  
Figure 3419: PRO82072  
Figure 3420: DNA325573, NM\_012101,  
gen.NM\_012101  
Figure 3421: PRO82073  
Figure 3422: DNA325574, NM\_058193,  
gen.NM\_058193  
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Figure 3425: PRO82075  
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gen.XM\_091786  
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gen.XM\_165390  
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gen.XM\_084525  
Figure 3429A-B: DNA325579, XM\_010494,  
gen.XM\_010494  
Figure 3430A-B: DNA325580, NM\_015064,  
gen.NM\_015064  
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Figure 3432: DNA325581, NM\_030775,  
gen.NM\_030775  
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Figure 3434: DNA297398, NM\_032642,  
gen.NM\_032642  
Figure 3435: PRO71031  
Figure 3436: DNA325582, XM\_017080,  
gen.XM\_017080  
Figure 3437: DNA325583, XM\_113739,  
gen.XM\_113739  
Figure 3438: PRO82080  
Figure 3439: DNA325584, NM\_002014,

gen.NM\_002014  
Figure 3440: PRO59262  
Figure 3441: DNA325585, XM\_096661,  
gen.XM\_096661  
Figure 3442: DNA325586, NM\_018463,  
gen.NM\_018463  
Figure 3443: PRO82082  
Figure 3444: DNA325587, NM\_021953,  
gen.NM\_021953  
Figure 3445: PRO82083  
Figure 3446: DNA325588, NM\_031465,  
gen.NM\_031465  
Figure 3447: PRO82084  
Figure 3448: DNA325589, NM\_005002,  
gen.NM\_005002  
Figure 3449: PRO82085  
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Figure 3451: DNA325591, XM\_116926,  
gen.XM\_116926  
Figure 3452: DNA88114, NM\_001734,  
gen.NM\_001734  
Figure 3453: PRO2660  
Figure 3454: DNA325592, XM\_058574,  
gen.XM\_058574  
Figure 3455: DNA325593, NM\_007273,  
gen.NM\_007273  
Figure 3456: PRO36970  
Figure 3457A-B: DNA325594, XM\_032588,  
gen.XM\_032588  
Figure 3458: DNA325595, NM\_001975,  
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Figure 3459: PRO38010  
Figure 3460: DNA325596, NM\_000365,  
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Figure 3461: PRO69549  
Figure 3462: DNA325597, XM\_032614,  
gen.XM\_032614  
Figure 3463: DNA325598, NM\_002075,  
gen.NM\_002075  
Figure 3464: PRO82091  
Figure 3465: DNA325599, XM\_165910,  
gen.XM\_165910  
Figure 3466: DNA151827, NM\_005439,  
gen.NM\_005439  
Figure 3467: PRO12902  
Figure 3468A-B: DNA254624, NM\_001273,  
gen.NM\_001273  
Figure 3469: PRO49726  
Figure 3470: DNA325600, NM\_015438,  
gen.NM\_015438  
Figure 3471: PRO82093  
Figure 3472: DNA325601, XM\_033263,  
gen.XM\_033263  
Figure 3473: DNA225632, NM\_002046,  
gen.NM\_002046

Figure 3474: PRO36095  
Figure 3475A-B: DNA325602, XM\_006958,  
gen.XM\_006958  
Figure 3476: DNA83180, NM\_002342,  
gen.NM\_002342  
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gen.NM\_001038  
Figure 3479: PRO4841  
Figure 3480: DNA188396, NM\_001065,  
gen.NM\_001065  
Figure 3481: PRO21924  
Figure 3482A-C: DNA325603, XM\_006947,  
gen.XM\_006947  
Figure 3483A-B: DNA325604, XM\_006936,  
gen.XM\_006936  
Figure 3484: PRO82097  
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gen.XM\_006925  
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gen.XM\_096630  
Figure 3487: PRO82099  
Figure 3488: DNA325607, XM\_084901,  
gen.XM\_084901  
Figure 3489: DNA226028, NM\_002355,  
gen.NM\_002355  
Figure 3490: PRO36491  
Figure 3491: DNA325608, XM\_031807,  
gen.XM\_031807  
Figure 3492: PRO82101  
Figure 3493A-B: DNA325609, XM\_049663,  
gen.XM\_049663  
Figure 3494: DNA325610, XM\_012159,  
gen.XM\_012159  
Figure 3495: DNA325611, XM\_084922,  
gen.XM\_084922  
Figure 3496: DNA325612, NM\_031289,  
gen.NM\_031289  
Figure 3497: PRO82104  
Figure 3498: DNA226771, NM\_003979,  
gen.NM\_003979  
Figure 3499: PRO37234  
Figure 3500: DNA325613, XM\_084918,  
gen.XM\_084918  
Figure 3501: DNA325614, NM\_007178,  
gen.NM\_007178  
Figure 3502: PRO82106  
Figure 3503: DNA325615, XM\_041100,  
gen.XM\_041100  
Figure 3504A-B: DNA325616, XM\_058567,  
gen.XM\_058567  
Figure 3505: PRO82107  
Figure 3506A-B: DNA325617, XM\_166605,  
gen.XM\_166605  
Figure 3507: DNA325618, XM\_029805,  
gen.XM\_029805

Figure 3508: PRO82109  
Figure 3509: DNA325619, NM\_005889,  
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Figure 3510: PRO82110  
Figure 3511: DNA256072, NM\_001644,  
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Figure 3512: PRO51121  
Figure 3513: DNA325620, NM\_018686,  
gen.NM\_018686  
Figure 3514: PRO82111  
Figure 3515: DNA325621, XM\_084770,  
gen.XM\_084770  
Figure 3516: PRO82112  
Figure 3517: DNA325622, NM\_018048,  
gen.NM\_018048  
Figure 3518: PRO82113  
Figure 3519: DNA325623, XM\_113730,  
gen.XM\_113730  
Figure 3520: DNA150978, NM\_007244,  
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Figure 3521: PRO11601  
Figure 3522: DNA325624, NM\_006250,  
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Figure 3523: PRO82115  
Figure 3524: DNA79313, NM\_005042,  
gen.NM\_005042  
Figure 3525: PRO2555  
Figure 3526: DNA150997, NM\_004982,  
gen.NM\_004982  
Figure 3527: PRO12573  
Figure 3528: DNA325625, XM\_050074,  
gen.XM\_050074  
Figure 3529: DNA325626, NM\_024854,  
gen.NM\_024854  
Figure 3530: PRO82117  
Figure 3531: DNA325627, XM\_084807,  
gen.XM\_084807  
Figure 3532: DNA325628, XM\_165906,  
gen.XM\_165906  
Figure 3533A-B: DNA325629, XM\_038659,  
gen.XM\_038659  
Figure 3534: PRO82120  
Figure 3535: DNA325630, XM\_006694,  
gen.XM\_006694  
Figure 3536: DNA325631, XM\_006748,  
gen.XM\_006748  
Figure 3537: PRO82122  
Figure 3538: DNA325632, XM\_016640,  
gen.XM\_016640  
Figure 3539: DNA325633, XM\_096146,  
gen.XM\_096146  
Figure 3540A-B: DNA325634, XM\_084841,  
gen.XM\_084841  
Figure 3541: PRO82125  
Figure 3542: DNA325635, XM\_090218,  
gen.XM\_090218

Figure 3543: DNA325636, XM\_012272,  
gen.XM\_012272  
Figure 3544: PRO82127  
Figure 3545A-B: DNA325637, XM\_056481,  
gen.XM\_056481  
Figure 3546: DNA325638, NM\_006262,  
gen.NM\_006262  
Figure 3547: PRO82129  
Figure 3548: DNA325639, NM\_018113,  
gen.NM\_018113  
Figure 3549: PRO82130  
Figure 3550: DNA271344, NM\_001659,  
gen.NM\_001659  
Figure 3551: PRO59647  
Figure 3552: DNA325640, NM\_017822,  
gen.NM\_017822  
Figure 3553: PRO82131  
Figure 3554A-E: DNA325641, XM\_028760,  
gen.XM\_028760  
Figure 3555: DNA272379, NM\_002733,  
gen.NM\_002733  
Figure 3556: PRO60634  
Figure 3557: DNA325642, XM\_084866,  
gen.XM\_084866  
Figure 3558: PRO82133  
Figure 3559: DNA325643, XM\_006826,  
gen.XM\_006826  
Figure 3560: DNA325644, XM\_113719,  
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Figure 3561: DNA325645, XM\_028662,  
gen.XM\_028662  
Figure 3562: DNA325646, XM\_035497,  
gen.XM\_035497  
Figure 3563: PRO82137  
Figure 3564: DNA325647, XM\_035490,  
gen.XM\_035490  
Figure 3565: PRO82138  
Figure 3566: DNA325648, NM\_013277,  
gen.NM\_013277  
Figure 3567: PRO82139  
Figure 3568: DNA325649, NM\_003076,  
gen.NM\_003076  
Figure 3569: PRO82140  
Figure 3570: DNA325650, XM\_115117,  
gen.XM\_115117  
Figure 3571: DNA325651, XM\_035485,  
gen.XM\_035485  
Figure 3572A-B: DNA325652, NM\_016357,  
gen.NM\_016357  
Figure 3573: PRO82143  
Figure 3574: DNA325653, NM\_005171,  
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Figure 3577: PRO4348

Figure 3578: DNA325655, XM\_096620, gen.XM\_096620  
Figure 3579: DNA325656, XM\_165905, gen.XM\_165905  
Figure 3580: DNA325657, XM\_015481, gen.XM\_015481  
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Figure 3582: DNA325659, XM\_084885, gen.XM\_084885  
Figure 3583: DNA325660, XM\_084884, gen.XM\_084884  
Figure 3584: DNA325661, XM\_113726, gen.XM\_113726  
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Figure 3591: DNA270458, NM\_002273, gen.NM\_002273  
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Figure 3596: DNA325666, XM\_015468, gen.XM\_015468  
Figure 3597: PRO82155  
Figure 3598: DNA325667, XM\_012162, gen.XM\_012162  
Figure 3599: DNA325668, XM\_084789, gen.XM\_084789  
Figure 3600: DNA196351, NM\_002178, gen.NM\_002178  
Figure 3601: PRO3449  
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Figure 3603: PRO82158  
Figure 3604: DNA325670, NM\_015665, gen.NM\_015665  
Figure 3605: PRO82159  
Figure 3606: DNA325671, NM\_014311, gen.NM\_014311  
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Figure 3608: DNA325672, XM\_096606, gen.XM\_096606  
Figure 3609: PRO82161  
Figure 3610: DNA325673, NM\_018457, gen.NM\_018457

Figure 3611: PRO82162  
Figure 3612: DNA325674, NM\_031157, gen.NM\_031157  
Figure 3613: PRO82163  
Figure 3614: DNA325675, NM\_004178, gen.NM\_004178  
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Figure 3616: DNA325676, NM\_134323, gen.NM\_134323  
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Figure 3621: PRO70453  
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Figure 3625: PRO82168  
Figure 3626: DNA325680, XM\_006710, gen.XM\_006710  
Figure 3627: PRO82169  
Figure 3628: DNA227094, NM\_005594, gen.NM\_005594  
Figure 3629: PRO37557  
Figure 3630: DNA325681, XM\_084824, gen.XM\_084824  
Figure 3631: DNA304783, NM\_014255, gen.NM\_014255  
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Figure 3636: DNA325685, NM\_006601, gen.NM\_006601  
Figure 3637: PRO82174  
Figure 3638: DNA325686, XM\_012182, gen.XM\_012182  
Figure 3639: PRO82175  
Figure 3640: DNA325687, XM\_048943, gen.XM\_048943  
Figure 3641: DNA325688, XM\_053164, gen.XM\_053164  
Figure 3642: DNA325689, XM\_048991, gen.XM\_048991  
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Figure 3644: PRO82179  
Figure 3645A-B: DNA325691, XM\_056346, gen.XM\_056346

Figure 3646: DNA325692, NM\_021019,  
gen.NM\_021019  
Figure 3647: PRO82181  
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gen.NM\_079423  
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Figure 3650: DNA325694, NM\_079425,  
gen.NM\_079425  
Figure 3651: PRO82183  
Figure 3652: DNA325695, XM\_049048,  
gen.XM\_049048  
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gen.NM\_021104  
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gen.NM\_001029  
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Figure 3658: DNA325698, XM\_001482,  
gen.XM\_001482  
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gen.XM\_049150  
Figure 3660: DNA325700, NM\_006928,  
gen.NM\_006928  
Figure 3661: PRO2846  
Figure 3662: DNA325701, XM\_056353,  
gen.XM\_056353  
Figure 3663: DNA325702, NM\_001780,  
gen.NM\_001780  
Figure 3664: PRO283  
Figure 3665: DNA325703, NM\_031479,  
gen.NM\_031479  
Figure 3666: PRO21773  
Figure 3667A-: DNA137231, NM\_005269,  
gen.NM\_005269  
Figure 3668: PRO9112  
Figure 3669: DNA325704, NM\_004990,  
gen.NM\_004990  
Figure 3670: PRO82188  
Figure 3671: DNA325705, XM\_058528,  
gen.XM\_058528  
Figure 3672: DNA325706, XM\_084801,  
gen.XM\_084801  
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gen.XM\_048603  
Figure 3675: PRO82191  
Figure 3676: DNA325708, NM\_133483,  
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Figure 3677: PRO82192  
Figure 3678: DNA79101, NM\_006812,  
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Figure 3679: PRO2549  
Figure 3680: DNA325709, XM\_096566,  
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Figure 3681: DNA325710, NM\_005981,

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Figure 3682: PRO4666  
Figure 3683: DNA325711, NM\_000075,  
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Figure 3684: PRO4873  
Figure 3685: DNA325712, NM\_052984,  
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Figure 3686: PRO82194  
Figure 3687: DNA325713, NM\_000785,  
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Figure 3688: PRO58440  
Figure 3689: DNA325714, NM\_005371,  
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Figure 3690: PRO82195  
Figure 3691: DNA325715, NM\_023032,  
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Figure 3692: PRO82196  
Figure 3693: DNA325716, NM\_023033,  
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Figure 3694: PRO82197  
Figure 3695: DNA325717, NM\_005726,  
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Figure 3696: PRO82198  
Figure 3697: DNA325718, NM\_006576,  
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Figure 3698: PRO82199  
Figure 3699A-B: DNA325719, XM\_096038,  
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Figure 3700: DNA325720, XM\_056681,  
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Figure 3701: PRO82201  
Figure 3702: DNA325721, XM\_084909,  
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Figure 3703: PRO82202  
Figure 3704: DNA325722, XM\_004098,  
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Figure 3705: DNA325723, XM\_084912,  
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Figure 3706: PRO82204  
Figure 3707: DNA325724, XM\_040221,  
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Figure 3708: DNA325725, XM\_016605,  
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Figure 3709: PRO82206  
Figure 3710: DNA325726, XM\_017508,  
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Figure 3711: PRO82207  
Figure 3712: DNA325727, NM\_032338,  
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Figure 3713: PRO82208  
Figure 3714A-B: DNA325728, XM\_052460,  
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Figure 3715: DNA325729, XM\_083866,  
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Figure 3716: PRO82210  
Figure 3717: DNA304694, NM\_020401,

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Figure 3718: PRO71120  
Figure 3719: DNA325730, XM\_052474,  
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Figure 3720: DNA227474, NM\_015646,  
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Figure 3721: PRO37937  
Figure 3722: DNA325731, XM\_053952,  
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Figure 3723: PRO82212  
Figure 3724: DNA227171, NM\_014515,  
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Figure 3725: PRO37634  
Figure 3726: DNA325732, XM\_046041,  
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Figure 3727: DNA271492, NM\_006530,  
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Figure 3728: PRO59785  
Figure 3729: DNA226014, NM\_000239,  
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Figure 3730: PRO36477  
Figure 3731: DNA325733, XM\_084645,  
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Figure 3732A-B: DNA325734, XM\_039395,  
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Figure 3733: PRO82213  
Figure 3734: DNA325736, XM\_040644,  
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Figure 3735: PRO82214  
Figure 3736A-B: DNA325737, XM\_006578,  
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Figure 3737: DNA325738, XM\_038308,  
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Figure 3738: PRO82215  
Figure 3739: DNA325739, XM\_096597,  
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Figure 3740: DNA325740, NM\_001920,  
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Figure 3741: PRO2841  
Figure 3742: DNA325741, NM\_133503,  
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Figure 3743: PRO2841  
Figure 3744: DNA325742, NM\_133504,  
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Figure 3745: PRO82218  
Figure 3746: DNA325743, NM\_133505,  
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Figure 3747: PRO82219  
Figure 3748: DNA325744, NM\_133507,  
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Figure 3749: PRO82220  
Figure 3750: DNA325745, NM\_133506,  
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Figure 3751: PRO82221  
Figure 3752: DNA325746, NM\_002345,  
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Figure 3753: PRO9987  
Figure 3754: DNA325747, XM\_167518,  
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Figure 3755: DNA325748, XM\_052542,  
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Figure 3756: PRO82223  
Figure 3757: DNA325749, NM\_003877,  
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Figure 3758: PRO12839  
Figure 3759: DNA325750, XM\_012219,  
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Figure 3760: PRO69473  
Figure 3761: DNA325751, XM\_012145,  
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Figure 3762: PRO82224  
Figure 3763: DNA274361, NM\_000895,  
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Figure 3764: PRO62273  
Figure 3765: DNA325752, XM\_006887,  
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Figure 3766: DNA325753, XM\_006589,  
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Figure 3767: DNA325754, XM\_090458,  
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Figure 3768: PRO82227  
Figure 3769: DNA325755, XM\_052641,  
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Figure 3770: PRO82228  
Figure 3771A-B: DNA325756, XM\_049211,  
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Figure 3772: DNA325757, XM\_049201,  
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Figure 3773: DNA325758, XM\_058556,  
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Figure 3774: DNA325759, XM\_083864,  
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Figure 3775: DNA325760, XM\_062437,  
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Figure 3776: PRO82232  
Figure 3777: DNA254777, NM\_014325,  
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Figure 3778: PRO49875  
Figure 3779: DNA325761, XM\_090413,  
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Figure 3780: PRO82233  
Figure 3781: DNA325762, NM\_000970,  
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Figure 3782: PRO82234  
Figure 3783: DNA325763, XM\_084800,  
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Figure 3784: PRO82235  
Figure 3785: DNA325764, NM\_006817,  
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Figure 3786: PRO70694  
Figure 3787A-C: DNA325765, XM\_083892,  
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Figure 3788A-B: DNA325766, XM\_084941,  
gen.XM\_084941  
Figure 3789: PRO82237  
Figure 3790A-B: DNA325767, NM\_057169,  
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Figure 3791: PRO82238  
Figure 3792A-B: DNA325768, NM\_014776,  
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Figure 3793: PRO82239  
Figure 3794: DNA325769, NM\_032904,  
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Figure 3795: PRO82240  
Figure 3796A-B: DNA325770, XM\_007003,  
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Figure 3797: DNA325771, XM\_007002,  
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Figure 3798: DNA325772, XM\_056996,  
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Figure 3799: PRO82243  
Figure 3800: DNA325773, XM\_084946,  
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Figure 3801: PRO82244  
Figure 3802: DNA325775, XM\_027102,  
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Figure 3803: PRO82245  
Figure 3804: DNA325776, XM\_084948,  
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Figure 3805: DNA325777, NM\_007062,  
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Figure 3806: PRO82247  
Figure 3807: DNA325778, NM\_006825,  
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Figure 3808: PRO82248  
Figure 3809: DNA325779, XM\_115197,  
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Figure 3810: DNA325780, NM\_017901,  
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Figure 3811: PRO82250  
Figure 3812: DNA325781, NM\_032814,  
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Figure 3813: PRO82252  
Figure 3814: DNA325782, XM\_084889,  
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Figure 3815: PRO82253  
Figure 3816: DNA325783, NM\_002567,  
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Figure 3817: PRO59001  
Figure 3818: DNA325784, XM\_084808,  
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Figure 3819: DNA325785, XM\_096572,  
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Figure 3820: PRO82255  
Figure 3821: DNA325786, XM\_045010,  
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Figure 3822: PRO82256  
Figure 3823: DNA270677, NM\_014868,

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Figure 3824: PRO59042  
Figure 3825: DNA325787, XM\_052893,  
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Figure 3826A-B: DNA325788, XM\_045802,  
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Figure 3827: DNA302016, NM\_001002,  
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Figure 3828: PRO70989  
Figure 3829: DNA325789, NM\_053275,  
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Figure 3830: PRO70989  
Figure 3831: DNA325790, NM\_006253,  
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Figure 3832: PRO82259  
Figure 3833: DNA325791, XM\_045187,  
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Figure 3834: DNA325792, XM\_045963,  
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Figure 3835: DNA325793, XM\_006595,  
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Figure 3836: DNA325794, XM\_012124,  
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Figure 3837: DNA325795, NM\_002813,  
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Figure 3838: PRO82263  
Figure 3839: DNA325796, NM\_019887,  
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Figure 3840: PRO69471  
Figure 3841A-B: DNA325797, XM\_038791,  
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Figure 3842: PRO82264  
Figure 3843: DNA325798, NM\_016638,  
gen.NM\_016638  
Figure 3844: PRO82265  
Figure 3845: DNA325799, XM\_116913,  
gen.XM\_116913  
Figure 3846: PRO82266  
Figure 3847: DNA325800, NM\_006815,  
gen.NM\_006815  
Figure 3848: PRO4793  
Figure 3849: DNA325801, XM\_006566,  
gen.XM\_006566  
Figure 3850: PRO82267  
Figure 3851: DNA325802, NM\_032656,  
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Figure 3852: PRO82268  
Figure 3853: DNA325803, XM\_055013,  
gen.XM\_055013  
Figure 3854: PRO82269  
Figure 3855: DNA325804, XM\_113737,  
gen.XM\_113737  
Figure 3856A-C: DNA325805, XM\_045602,  
gen.XM\_045602  
Figure 3857: DNA325806, XM\_087955,  
gen.XM\_087955

Figure 3858: PRO82272  
Figure 3859A-B: DNA325807, XM\_044334,  
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Figure 3860: PRO82273  
Figure 3861: DNA325808, XM\_012184,  
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Figure 3862: DNA325809, XM\_113702,  
gen.XM\_113702  
Figure 3863: PRO82275  
Figure 3864A-B: DNA270015, NM\_003453,  
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Figure 3865: PRO58410  
Figure 3866: DNA226853, NM\_004004,  
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Figure 3867: PRO37316  
Figure 3868: DNA325810, XM\_167911,  
gen.XM\_167911  
Figure 3869: DNA325811, XM\_167918,  
gen.XM\_167918  
Figure 3870: DNA325812, XM\_084982,  
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Figure 3871: PRO82278  
Figure 3872: DNA325813, NM\_024026,  
gen.NM\_024026  
Figure 3873: PRO82279  
Figure 3874: DNA325814, XM\_012638,  
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Figure 3875: PRO82280  
Figure 3876: DNA325815, XM\_167439,  
gen.XM\_167439  
Figure 3877: DNA325816, XM\_167906,  
gen.XM\_167906  
Figure 3878A-B: DNA325817, NM\_014778,  
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Figure 3879: PRO82283  
Figure 3880: DNA325818, XM\_169414,  
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Figure 3881A-B: DNA325819, NM\_006646,  
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Figure 3882: PRO82285  
Figure 3883: DNA325820, XM\_167892,  
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Figure 3884: DNA325821, NM\_015932,  
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Figure 3885: PRO82287  
Figure 3886: DNA325822, XM\_166273,  
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Figure 3887: DNA304669, NM\_002128,  
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Figure 3888: PRO71096  
Figure 3889: DNA325823, NM\_014887,  
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Figure 3890: PRO82289  
Figure 3891: DNA325824, NM\_002915,  
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Figure 3892: PRO82290

Figure 3893: DNA325825, XM\_085017,  
gen.XM\_085017  
Figure 3894: PRO82291  
Figure 3895: DNA325826, XM\_017432,  
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Figure 3896A-B: DNA270254, NM\_002015,  
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Figure 3897: PRO58642  
Figure 3898: DNA325827, NM\_005830,  
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Figure 3899: PRO58092  
Figure 3900: DNA281436, NM\_003295,  
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Figure 3901: PRO66275  
Figure 3902: DNA325828, XM\_038371,  
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Figure 3903A-B: DNA325829, XM\_165636,  
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Figure 3904: DNA325830, XM\_166266,  
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Figure 3905: PRO82295  
Figure 3906: DNA325831, NM\_014166,  
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Figure 3907: PRO82296  
Figure 3908: DNA325832, NM\_021999,  
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Figure 3909: PRO1869  
Figure 3910: DNA325833, NM\_030925,  
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Figure 3911: PRO82297  
Figure 3912: DNA274058, NM\_016119,  
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Figure 3913: PRO61999  
Figure 3914: DNA325834, NM\_032565,  
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Figure 3915: PRO11982  
Figure 3916: DNA325835, XM\_085044,  
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Figure 3917: DNA325836, XM\_165639,  
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Figure 3918: DNA325837, XM\_018399,  
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Figure 3919: PRO82300  
Figure 3920: DNA325838, XM\_058977,  
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Figure 3921: DNA325839, XM\_015840,  
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Figure 3922: PRO82302  
Figure 3923: DNA325840, XM\_007199,  
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Figure 3924: DNA325841, XM\_016351,  
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Figure 3925: DNA325842, XM\_041209,  
gen.XM\_041209  
Figure 3926: DNA325843, XM\_058611,  
gen.XM\_058611



Figure 3927: PRO82305  
Figure 3928: DNA325844, XM\_041473,  
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Figure 3929: PRO82306  
Figure 3930: DNA325845, XM\_032443,  
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Figure 3931: DNA325847, XM\_048957,  
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Figure 3932: DNA325848, XM\_015842,  
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Figure 3933: DNA325849, XM\_084997,  
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Figure 3934: PRO82311  
Figure 3935: DNA325850, NM\_024089,  
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Figure 3936: PRO82312  
Figure 3937A-B: DNA325851, XM\_049904,  
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Figure 3938: DNA325852, NM\_024537,  
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Figure 3939: PRO82314  
Figure 3940: DNA325853, NM\_023011,  
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Figure 3941: PRO82315  
Figure 3942: DNA325854, NM\_080687,  
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Figure 3943: PRO82316  
Figure 3944: DNA325855, XM\_041484,  
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Figure 3945: PRO82317  
Figure 3946A-B: DNA325856, XM\_113752,  
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Figure 3947: PRO82318  
Figure 3948: DNA325857, XM\_115215,  
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Figure 3949: DNA325858, XM\_046651,  
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Figure 3950: DNA325859, XM\_046648,  
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Figure 3951: DNA325860, XM\_046642,  
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Figure 3952: PRO10404  
Figure 3953: DNA325861, XM\_017914,  
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Figure 3954: PRO82321  
Figure 3955: DNA325862, XM\_085166,  
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Figure 3956: PRO82322  
Figure 3957: DNA325863, XM\_007316,  
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Figure 3958: DNA325864, XM\_007315,  
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Figure 3959: DNA325865, XM\_033251,  
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Figure 3960: DNA325866, NM\_024658,  
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Figure 3961: PRO82325  
Figure 3962: DNA210180, NM\_005132,  
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Figure 3963: PRO33717  
Figure 3964: DNA325867, XM\_033337,  
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Figure 3965: PRO82326  
Figure 3966: DNA325868, XM\_096772,  
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Figure 3967: DNA325869, XM\_007293,  
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Figure 3968: DNA325870, XM\_007288,  
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Figure 3969A-B: DNA325871, XM\_033391,  
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Figure 3970: PRO82329  
Figure 3971: DNA325872, NM\_017815,  
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Figure 3972: PRO82330  
Figure 3973: DNA325873, NM\_006109,  
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Figure 3974: PRO82331  
Figure 3975: DNA325874, XM\_033435,  
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Figure 3976: DNA225865, NM\_004995,  
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Figure 3977: PRO36328  
Figure 3978: DNA325875, XM\_058647,  
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Figure 3979: PRO82333  
Figure 3980: DNA325876, XM\_033445,  
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Figure 3981: DNA325877, NM\_005015,  
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Figure 3982: PRO82334  
Figure 3983: DNA325878, XM\_012377,  
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Figure 3984: DNA227321, NM\_001344,  
gen.NM\_001344  
Figure 3985: PRO37784  
Figure 3986: DNA325879, XM\_058646,  
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Figure 3987: DNA325880, XM\_085106,  
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Figure 3988: DNA325881, NM\_019852,  
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Figure 3989: PRO82338  
Figure 3990: DNA325882, XM\_012376,  
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Figure 3991: DNA325883, XM\_033553,  
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Figure 3992: DNA226105, NM\_002934,  
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Figure 3993: PRO36568  
Figure 3994: DNA325884, XM\_033595,  
gen.XM\_033595

Figure 3995: PRO2871  
Figure 3996: DNA325885, XM\_007491,  
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Figure 3997: DNA325886, NM\_001641,  
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Figure 3998: PRO82342  
Figure 3999: DNA325887, NM\_080648,  
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Figure 4000: PRO82343  
Figure 4001: DNA325888, NM\_080649,  
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Figure 4002: PRO82344  
Figure 4003: DNA325889, NM\_017807,  
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Figure 4004: PRO82345  
Figure 4005A-C: DNA325890, XM\_007488,  
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Figure 4006: DNA325891, NM\_021178,  
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Figure 4007: PRO82347  
Figure 4008: DNA325892, XM\_041235,  
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Figure 4009: PRO82348  
Figure 4010: DNA325893, NM\_002028,  
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Figure 4011: PRO82349  
Figure 4012: DNA325894, NM\_002083,  
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Figure 4013: PRO82350  
Figure 4014A-B: DNA325895, XM\_085127,  
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Figure 4015: PRO82351  
Figure 4016A-B: DNA325896, NM\_001530,  
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Figure 4017: PRO82352  
Figure 4018: DNA325897, XM\_058210,  
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Figure 4019: DNA325898, XM\_085141,  
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Figure 4022: DNA325900, NM\_002306,  
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Figure 4023: PRO82356  
Figure 4024: DNA325901, XM\_007328,  
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Figure 4025A-B: DNA325902, XM\_051712,  
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Figure 4026: PRO82357  
Figure 4027: DNA325903, XM\_007324,  
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Figure 4028: PRO82358  
Figure 4029: DNA325904, NM\_002863,  
gen.NM\_002863  
Figure 4030: PRO82359

Figure 4031: DNA325905, XM\_085125,  
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Figure 4032: DNA325906, XM\_031025,  
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Figure 4033: DNA325907, XM\_085066,  
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Figure 4034: DNA325908, XM\_096744,  
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Figure 4035: DNA325909, NM\_016445,  
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Figure 4036: PRO82364  
Figure 4037: DNA325910, NM\_016026,  
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Figure 4038: PRO82365  
Figure 4039: DNA325911, XM\_031074,  
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Figure 4040: DNA325912, NM\_001102,  
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Figure 4041: PRO82367  
Figure 4042: DNA225649, NM\_022137,  
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Figure 4043: PRO36112  
Figure 4044: DNA325913, XM\_085065,  
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Figure 4045: DNA325914, XM\_007441,  
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Figure 4046: DNA325915, NM\_006821,  
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Figure 4047: PRO82369  
Figure 4048: DNA325916, NM\_006432,  
gen.NM\_006432  
Figure 4049: PRO2066  
Figure 4050A-B: DNA325917, XM\_085151,  
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Figure 4051: PRO82370  
Figure 4052: DNA325918, NM\_002632,  
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Figure 4053: PRO82371  
Figure 4054: DNA325919, XM\_085162,  
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Figure 4055: DNA325920, NM\_012111,  
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Figure 4056: PRO82373  
Figure 4057: DNA325921, NM\_024824,  
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Figure 4058: PRO82374  
Figure 4059: DNA269498, NM\_002802,  
gen.NM\_002802  
Figure 4060: PRO57917  
Figure 4061: DNA325922, XM\_058677,  
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Figure 4062: PRO82375  
Figure 4063: DNA325923, NM\_006888,  
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Figure 4064: PRO4904  
Figure 4065: DNA325924, NM\_001275,

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Figure 4066: PRO2054  
Figure 4067: DNA325925, XM\_029288,  
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Figure 4068A-B: DNA325926, XM\_016487,  
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Figure 4069: DNA325927, NM\_020414,  
gen.NM\_020414  
Figure 4070: PRO62099  
Figure 4071: DNA325928, XM\_016486,  
gen.XM\_016486  
Figure 4072: DNA325929, XM\_007483,  
gen.XM\_007483  
Figure 4073: DNA325930, XM\_028358,  
gen.XM\_028358  
Figure 4074: DNA325931, XM\_028347,  
gen.XM\_028347  
Figure 4075: DNA325932, XM\_028322,  
gen.XM\_028322  
Figure 4076: PRO82381  
Figure 4077: DNA325933, XM\_056317,  
gen.XM\_056317  
Figure 4078: PRO82382  
Figure 4079: DNA151893, NM\_021966,  
gen.NM\_021966  
Figure 4080: PRO12916  
Figure 4081: DNA325934, XM\_007272,  
gen.XM\_007272  
Figure 4082: DNA325935, XM\_090914,  
gen.XM\_090914  
Figure 4083: PRO82383  
Figure 4084: DNA325936, NM\_022747,  
gen.NM\_022747  
Figure 4085: PRO82384  
Figure 4086: DNA325937, XM\_041014,  
gen.XM\_041014  
Figure 4087: PRO60575  
Figure 4088: DNA325938, NM\_003836,  
gen.NM\_003836  
Figure 4089: PRO82385  
Figure 4090A-B: DNA325939, XM\_040952,  
gen.XM\_040952  
Figure 4091: DNA325940, XM\_058618,  
gen.XM\_058618  
Figure 4092: DNA325941, NM\_005348,  
gen.NM\_005348  
Figure 4093: PRO82388  
Figure 4094: DNA325942, XM\_040942,  
gen.XM\_040942  
Figure 4095: DNA226324, NM\_014226,  
gen.NM\_014226  
Figure 4096: PRO36787  
Figure 4097A-B: DNA325943, XM\_007254,  
gen.XM\_007254  
Figure 4098A-B: DNA325944, NM\_001969,  
gen.NM\_001969

Figure 4099: PRO82391  
Figure 4100: DNA325945, XM\_040898,  
gen.XM\_040898  
Figure 4101: DNA325946, NM\_005432,  
gen.NM\_005432  
Figure 4102: PRO60070  
Figure 4103A-B: DNA325947, XM\_050278,  
gen.XM\_050278  
Figure 4104: PRO82393  
Figure 4105: DNA325948, XM\_113759,  
gen.XM\_113759  
Figure 4106: DNA325949, NM\_006427,  
gen.NM\_006427  
Figure 4107: PRO82395  
Figure 4108: DNA325950, NM\_021709,  
gen.NM\_021709  
Figure 4109: PRO82396  
Figure 4110: DNA103509, NM\_005163,  
gen.NM\_005163  
Figure 4111: PRO4836  
Figure 4112: DNA325951, NM\_017955,  
gen.NM\_017955  
Figure 4113: PRO82397  
Figure 4114: DNA325952, XM\_088588,  
gen.XM\_088588  
Figure 4115: DNA325953, XM\_060012,  
gen.XM\_060012  
Figure 4116: DNA325954, XM\_034953,  
gen.XM\_034953  
Figure 4117: PRO82400  
Figure 4118: DNA325955, XM\_058636,  
gen.XM\_058636  
Figure 4119: DNA325956, XM\_035014,  
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Figure 4120: DNA325957, XM\_088587,  
gen.XM\_088587  
Figure 4121: DNA325958, XM\_088589,  
gen.XM\_088589  
Figure 4122: DNA325959, XM\_071801,  
gen.XM\_071801  
Figure 4123: DNA325960, XM\_018054,  
gen.XM\_018054  
Figure 4124: DNA325961, XM\_091108,  
gen.XM\_091108  
Figure 4125A-B: DNA325962, XM\_039225,  
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Figure 4126: PRO82408  
Figure 4127: DNA325963, XM\_165921,  
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Figure 4128: PRO82409  
Figure 4129: DNA325964, XM\_007751,  
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Figure 4130: DNA325965, XM\_085203,  
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Figure 4131: PRO82411  
Figure 4132: DNA325966, XM\_085204,

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Figure 4133: DNA325967, XM\_012398,  
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Figure 4134A-B: DNA325968, XM\_036727,  
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Figure 4135: DNA325969, XM\_017240,  
gen.XM\_017240  
Figure 4136: DNA325970, NM\_020149,  
gen.NM\_020149  
Figure 4137: PRO82415  
Figure 4138A-B: DNA325971, XM\_031617,  
gen.XM\_031617  
Figure 4139A-B: DNA325972, NM\_001211,  
gen.NM\_001211  
Figure 4140: PRO82417  
Figure 4141A-B: DNA151831, NM\_004573,  
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Figure 4142: PRO12198  
Figure 4143: DNA325973, NM\_130468,  
gen.NM\_130468  
Figure 4144: PRO82418  
Figure 4145: DNA325974, XM\_031554,  
gen.XM\_031554  
Figure 4146: PRO82419  
Figure 4147: DNA325975, XM\_031515,  
gen.XM\_031515  
Figure 4148: DNA325976, NM\_024111,  
gen.NM\_024111  
Figure 4149: PRO82421  
Figure 4150: DNA325977, NM\_032196,  
gen.NM\_032196  
Figure 4151: PRO82422  
Figure 4152: DNA325978, NM\_016359,  
gen.NM\_016359  
Figure 4153: PRO82423  
Figure 4154: DNA325979, NM\_018454,  
gen.NM\_018454  
Figure 4155: PRO82424  
Figure 4156A-B: DNA325980, XM\_007545,  
gen.XM\_007545  
Figure 4157: DNA325981, XM\_091159,  
gen.XM\_091159  
Figure 4158: PRO82425  
Figure 4159: DNA325982, XM\_031718,  
gen.XM\_031718  
Figure 4160: DNA325983, XM\_085307,  
gen.XM\_085307  
Figure 4161: DNA227559, NM\_000070,  
gen.NM\_000070  
Figure 4162: PRO38022  
Figure 4163A-B: DNA325984, XM\_113823,  
gen.XM\_113823  
Figure 4164: PRO82428  
Figure 4165: DNA325985, XM\_016713,  
gen.XM\_016713  
Figure 4166: PRO82429

Figure 4167A-B: DNA325986, XM\_007531,  
gen.XM\_007531  
Figure 4168: DNA325987, NM\_014444,  
gen.NM\_014444  
Figure 4169: PRO82431  
Figure 4170A-B: DNA227206, NM\_005657,  
gen.NM\_005657  
Figure 4171: PRO37669  
Figure 4172: DNA325988, NM\_020990,  
gen.NM\_020990  
Figure 4173: PRO82432  
Figure 4174: DNA325989, NM\_005313,  
gen.NM\_005313  
Figure 4175: PRO2732  
Figure 4176: DNA325990, NM\_005770,  
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Figure 4177: PRO82433  
Figure 4178: DNA325991, NM\_004048,  
gen.NM\_004048  
Figure 4179: PRO4379  
Figure 4180: DNA325992, XM\_032403,  
gen.XM\_032403  
Figure 4181: PRO82434  
Figure 4182: DNA219233, NM\_014335,  
gen.NM\_014335  
Figure 4183: PRO34557  
Figure 4184A-C: DNA325993, XM\_034890,  
gen.XM\_034890  
Figure 4185: PRO82435  
Figure 4186: DNA325994, XM\_058684,  
gen.XM\_058684  
Figure 4187: DNA325995, NM\_003104,  
gen.NM\_003104  
Figure 4188: PRO82437  
Figure 4189: DNA325996, XM\_007651,  
gen.XM\_007651  
Figure 4190: PRO82438  
Figure 4191: DNA325997, XM\_090991,  
gen.XM\_090991  
Figure 4192: PRO82439  
Figure 4193: DNA325998, NM\_016304,  
gen.NM\_016304  
Figure 4194: PRO82440  
Figure 4195: DNA325999, NM\_017610,  
gen.NM\_017610  
Figure 4196: PRO82441  
Figure 4197: DNA326000, NM\_004701,  
gen.NM\_004701  
Figure 4198: PRO82442  
Figure 4199A-B: DNA326001, XM\_012418,  
gen.XM\_012418  
Figure 4200: DNA326002, XM\_039702,  
gen.XM\_039702  
Figure 4201: PRO82444  
Figure 4202: DNA326003, XM\_113266,  
gen.XM\_113266

Figure 4203: DNA326004, NM\_001218,  
gen.NM\_001218  
Figure 4204: PRO54594  
Figure 4205: DNA326005, NM\_015920,  
gen.NM\_015920  
Figure 4206: PRO82446  
Figure 4207: DNA326006, XM\_113268,  
gen.XM\_113268  
Figure 4208: DNA255340, NM\_017684,  
gen.NM\_017684  
Figure 4209: PRO50409  
Figure 4210: DNA326007, NM\_002537,  
gen.NM\_002537  
Figure 4211: DNA326008, XM\_085283,  
gen.XM\_085283  
Figure 4212: PRO82448  
Figure 4213: DNA326009, XM\_016985,  
gen.XM\_016985  
Figure 4214: DNA234442, NM\_014736,  
gen.NM\_014736  
Figure 4215: PRO38852  
Figure 4216: DNA326010, NM\_022048,  
gen.NM\_022048  
Figure 4217: PRO82450  
Figure 4218: DNA326011, NM\_000942,  
gen.NM\_000942  
Figure 4219: PRO2720  
Figure 4220: DNA326012, XM\_050964,  
gen.XM\_050964  
Figure 4221: DNA326013, XM\_007623,  
gen.XM\_007623  
Figure 4222A-B: DNA326014, NM\_133375,  
gen.NM\_133375  
Figure 4223: PRO82453  
Figure 4224: DNA226646, NM\_017882,  
gen.NM\_017882  
Figure 4225: PRO37109  
Figure 4226: DNA326015, NM\_015322,  
gen.NM\_015322  
Figure 4227: PRO82454  
Figure 4228: DNA326016, NM\_001003,  
gen.NM\_001003  
Figure 4229: PRO82455  
Figure 4230A-B: DNA326017, XM\_051463,  
gen.XM\_051463  
Figure 4231: PRO82456  
Figure 4232: DNA326018, NM\_018357,  
gen.NM\_018357  
Figure 4233: PRO82457  
Figure 4234: DNA326019, XM\_063639,  
gen.XM\_063639  
Figure 4235: PRO82458  
Figure 4236: DNA326020, XM\_085249,  
gen.XM\_085249  
Figure 4237: DNA326021, XM\_016076,  
gen.XM\_016076

Figure 4238: PRO82460  
Figure 4239: DNA326022, XM\_015366,  
gen.XM\_015366  
Figure 4240: PRO82461  
Figure 4241: DNA326023, XM\_096060,  
gen.XM\_096060  
Figure 4242: DNA287331, NM\_002654,  
gen.NM\_002654  
Figure 4243: PRO69595  
Figure 4244: DNA326024, XM\_037778,  
gen.XM\_037778  
Figure 4245: DNA326025, XM\_096842,  
gen.XM\_096842  
Figure 4246: DNA326026, NM\_022369,  
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Figure 4247: PRO82465  
Figure 4248: DNA326027, NM\_032907,  
gen.NM\_032907  
Figure 4249: PRO82466  
Figure 4250: DNA326028, XM\_058699,  
gen.XM\_058699  
Figure 4251: DNA326029, XM\_118637,  
gen.XM\_118637  
Figure 4252: DNA326030, XM\_053585,  
gen.XM\_053585  
Figure 4253: PRO82469  
Figure 4254: DNA326031, XM\_085239,  
gen.XM\_085239  
Figure 4255: PRO82470  
Figure 4256: DNA326032, XM\_034897,  
gen.XM\_034897  
Figure 4257A-B: DNA326033, XM\_057020,  
gen.XM\_057020  
Figure 4258: PRO82472  
Figure 4259: DNA326034, NM\_000743,  
gen.NM\_000743  
Figure 4260: PRO61219  
Figure 4261: DNA326035, NM\_002789,  
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Figure 4262: PRO60499  
Figure 4263: DNA326036, XM\_091100,  
gen.XM\_091100  
Figure 4264: PRO82473  
Figure 4265: DNA255370, NM\_012170,  
gen.NM\_012170  
Figure 4266: PRO50438  
Figure 4267: DNA273014, NM\_000126,  
gen.NM\_000126  
Figure 4268: PRO61085  
Figure 4269: DNA326037, XM\_044565,  
gen.XM\_044565  
Figure 4270: DNA326038, NM\_025234,  
gen.NM\_025234  
Figure 4271: PRO82475  
Figure 4272: DNA326039, XM\_044569,  
gen.XM\_044569

Figure 4273: DNA326040, NM\_005724,  
gen.NM\_005724  
Figure 4274: PRO730  
Figure 4275: DNA326041, XM\_049354,  
gen.XM\_049354  
Figure 4276: PRO82477  
Figure 4277: DNA326042, NM\_007364,  
gen.NM\_007364  
Figure 4278: DNA326043, XM\_044593,  
gen.XM\_044593  
Figure 4279: DNA326044, NM\_006791,  
gen.NM\_006791  
Figure 4280: PRO82479  
Figure 4281: DNA326045, XM\_060042,  
gen.XM\_060042  
Figure 4282: DNA326046, XM\_085215,  
gen.XM\_085215  
Figure 4283: DNA326047, NM\_001021,  
gen.NM\_001021  
Figure 4284: PRO82482  
Figure 4285: DNA326048, XM\_031404,  
gen.XM\_031404  
Figure 4286: DNA326049, XM\_096844,  
gen.XM\_096844  
Figure 4287: DNA326050, XM\_045681,  
gen.XM\_045681  
Figure 4288: PRO82485  
Figure 4289: DNA326051, XM\_085280,  
gen.XM\_085280  
Figure 4290: DNA326052, NM\_022839,  
gen.NM\_022839  
Figure 4291: PRO82487  
Figure 4292: DNA326053, XM\_031354,  
gen.XM\_031354  
Figure 4293: DNA326054, NM\_002168,  
gen.NM\_002168  
Figure 4294: PRO82489  
Figure 4295: DNA326055, XM\_031292,  
gen.XM\_031292  
Figure 4296: DNA326056, NM\_022566,  
gen.NM\_022566  
Figure 4297: PRO82491  
Figure 4298A-B: DNA326057, XM\_051860,  
gen.XM\_051860  
Figure 4299: PRO82492  
Figure 4300: DNA275144, NM\_000137,  
gen.NM\_000137  
Figure 4301: PRO62852  
Figure 4302: DNA326058, NM\_016645,  
gen.NM\_016645  
Figure 4303: PRO82493  
Figure 4304: DNA326059, XM\_044523,  
gen.XM\_044523  
Figure 4305: DNA150485, NM\_006384,  
gen.NM\_006384  
Figure 4306: PRO12774

Figure 4307A-B: DNA326060, XM\_044533,  
gen.XM\_044533  
Figure 4308: PRO82495  
Figure 4309A-C: DNA326061, XM\_054900,  
gen.XM\_054900  
Figure 4310: DNA326062, NM\_032162,  
gen.NM\_032162  
Figure 4311A-B: DNA326063, XM\_015835,  
gen.XM\_015835  
Figure 4312: DNA326064, NM\_018668,  
gen.NM\_018668  
Figure 4313: PRO82499  
Figure 4314: DNA326065, XM\_085262,  
gen.XM\_085262  
Figure 4315: DNA326066, NM\_033544,  
gen.NM\_033544  
Figure 4316: PRO82501  
Figure 4317: DNA326067, XM\_049372,  
gen.XM\_049372  
Figure 4318: PRO82502  
Figure 4319: DNA326068, XM\_017971,  
gen.XM\_017971  
Figure 4320: DNA275181, NM\_003090,  
gen.NM\_003090  
Figure 4321: PRO62882  
Figure 4322: DNA326069, XM\_012462,  
gen.XM\_012462  
Figure 4323A-B: DNA326070, XM\_085525,  
gen.XM\_085525  
Figure 4324: PRO82505  
Figure 4325: DNA326071, XM\_165923,  
gen.XM\_165923  
Figure 4326: DNA326072, XM\_113836,  
gen.XM\_113836  
Figure 4327: DNA326073, NM\_017668,  
gen.NM\_017668  
Figure 4328: PRO82508  
Figure 4329: DNA326074, XM\_027309,  
gen.XM\_027309  
Figure 4330: PRO82509  
Figure 4331: DNA326075, XM\_018432,  
gen.XM\_018432  
Figure 4332: PRO82510  
Figure 4333: DNA326076, XM\_115352,  
gen.XM\_115352  
Figure 4334: DNA326077, XM\_027365,  
gen.XM\_027365  
Figure 4335: DNA326078, NM\_016641,  
gen.NM\_016641  
Figure 4336: PRO38464  
Figure 4337: DNA326079, XM\_058796,  
gen.XM\_058796  
Figure 4338: DNA326080, XM\_017984,  
gen.XM\_017984  
Figure 4339: PRO82513  
Figure 4340: DNA326081, NM\_020677,

gen.NM\_020677  
Figure 4341: PRO82514  
Figure 4342: DNA326082, XM\_036680,  
gen.XM\_036680  
Figure 4343: PRO37961  
Figure 4344A-B: DNA326083, XM\_048119,  
gen.XM\_048119  
Figure 4345: PRO82515  
Figure 4346: DNA326084, NM\_024589,  
gen.NM\_024589  
Figure 4347: PRO82516  
Figure 4348: DNA326085, XM\_050534,  
gen.XM\_050534  
Figure 4349: PRO82517  
Figure 4350: DNA326086, NM\_024571,  
gen.NM\_024571  
Figure 4351: PRO82518  
Figure 4352: DNA326087, XM\_027558,  
gen.XM\_027558  
Figure 4353: DNA326088, XM\_008126,  
gen.XM\_008126  
Figure 4354: DNA326089, NM\_000517,  
gen.NM\_000517  
Figure 4355: PRO3629  
Figure 4356: DNA326090, NM\_000558,  
gen.NM\_000558  
Figure 4357: PRO3629  
Figure 4358: DNA326091, NM\_018032,  
gen.NM\_018032  
Figure 4359: PRO38311  
Figure 4360: DNA273839, NM\_006428,  
gen.NM\_006428  
Figure 4361: PRO61799  
Figure 4362A-B: DNA256844, NM\_005632,  
gen.NM\_005632  
Figure 4363: PRO51775  
Figure 4364: DNA326092, XM\_083939,  
gen.XM\_083939  
Figure 4365: PRO82521  
Figure 4366: DNA326093, NM\_058192,  
gen.NM\_058192  
Figure 4367: PRO82522  
Figure 4368: DNA326094, XM\_027412,  
gen.XM\_027412  
Figure 4369: PRO82523  
Figure 4370: DNA256886, NM\_014587,  
gen.NM\_014587  
Figure 4371: PRO51815  
Figure 4372A-B: DNA326095, NM\_001287,  
gen.NM\_001287  
Figure 4373: PRO38480  
Figure 4374: DNA254781, NM\_016111,  
gen.NM\_016111  
Figure 4375: PRO49879  
Figure 4376: DNA326096, XM\_034586,  
gen.XM\_034586

Figure 4377: PRO82524  
Figure 4378: DNA326097, NM\_023936,  
gen.NM\_023936  
Figure 4379: PRO82525  
Figure 4380: DNA326098, XM\_034590,  
gen.XM\_034590  
Figure 4381: PRO82526  
Figure 4382: DNA326099, NM\_002952,  
gen.NM\_002952  
Figure 4383: PRO82527  
Figure 4384: DNA326100, NM\_006453,  
gen.NM\_006453  
Figure 4385: PRO82528  
Figure 4386: DNA326101, NM\_014353,  
gen.NM\_014353  
Figure 4387: PRO82529  
Figure 4388: DNA326102, NM\_032271,  
gen.NM\_032271  
Figure 4389: PRO82530  
Figure 4390: DNA326103, XM\_028848,  
gen.XM\_028848  
Figure 4391: PRO82531  
Figure 4392: DNA326104, NM\_006711,  
gen.NM\_006711  
Figure 4393: PRO82532  
Figure 4394: DNA326105, NM\_080594,  
gen.NM\_080594  
Figure 4395: PRO82533  
Figure 4396: DNA326106, NM\_024339,  
gen.NM\_024339  
Figure 4397: PRO82534  
Figure 4398: DNA326107, NM\_016639,  
gen.NM\_016639  
Figure 4399: PRO12683  
Figure 4400: DNA326108, NM\_021195,  
gen.NM\_021195  
Figure 4401: PRO82535  
Figure 4402: DNA326109, NM\_004203,  
gen.NM\_004203  
Figure 4403: PRO82536  
Figure 4404: DNA326110, XM\_058784,  
gen.XM\_058784  
Figure 4405: PRO82537  
Figure 4406: DNA326111, NM\_024507,  
gen.NM\_024507  
Figure 4407: PRO82538  
Figure 4408: DNA326112, NM\_006799,  
gen.NM\_006799  
Figure 4409: PRO303  
Figure 4410A-C: DNA326113, XM\_036528,  
gen.XM\_036528  
Figure 4411: DNA326114, NM\_025108,  
gen.NM\_025108  
Figure 4412: PRO82540  
Figure 4413A-C: DNA326115, XM\_165411,  
gen.XM\_165411

Figure 4414: DNA326116, NM\_016292,  
gen.NM\_016292  
Figure 4415: PRO82542  
Figure 4416: DNA326117, NM\_002484,  
gen.NM\_002484  
Figure 4417: PRO82543  
Figure 4418: DNA326118, XM\_113845,  
gen.XM\_113845  
Figure 4419: PRO82544  
Figure 4420: DNA326119, XM\_113843,  
gen.XM\_113843  
Figure 4421: DNA97293, NM\_003366,  
gen.NM\_003366  
Figure 4422: PRO3640  
Figure 4423: DNA326120, NM\_006110,  
gen.NM\_006110  
Figure 4424: PRO82546  
Figure 4425: DNA326121, XM\_085445,  
gen.XM\_085445  
Figure 4426: DNA326122, XM\_113876,  
gen.XM\_113876  
Figure 4427A-B: DNA326123, XM\_055195,  
gen.XM\_055195  
Figure 4428: PRO82548  
Figure 4429: DNA326124, XM\_113291,  
gen.XM\_113291  
Figure 4430A-B: DNA326125, XM\_007988,  
gen.XM\_007988  
Figure 4431: DNA326126, XM\_113874,  
gen.XM\_113874  
Figure 4432: DNA326127, XM\_102377,  
gen.XM\_102377  
Figure 4433: PRO82551  
Figure 4434: DNA326128, XM\_086278,  
gen.XM\_086278  
Figure 4435: DNA326129, XM\_085452,  
gen.XM\_085452  
Figure 4436: DNA326130, NM\_018054,  
gen.NM\_018054  
Figure 4437: PRO82554  
Figure 4438A-B: DNA326131, XM\_056260,  
gen.XM\_056260  
Figure 4439: PRO82555  
Figure 4440: DNA326132, NM\_032626,  
gen.NM\_032626  
Figure 4441: PRO82556  
Figure 4442: DNA326133, NM\_005030,  
gen.NM\_005030  
Figure 4443: PRO82557  
Figure 4444: DNA326134, NM\_032486,  
gen.NM\_032486  
Figure 4445: PRO82558  
Figure 4446: DNA289522, NM\_005003,  
gen.NM\_005003  
Figure 4447: PRO70276  
Figure 4448: DNA326135, XM\_085340,

gen.XM\_085340  
Figure 4449: DNA326136, NM\_003752,  
gen.NM\_003752  
Figure 4450: PRO60325  
Figure 4451: DNA326137, NM\_012248,  
gen.NM\_012248  
Figure 4452: PRO82560  
Figure 4453A-B: DNA326138, XM\_046035,  
gen.XM\_046035  
Figure 4454: DNA326139, NM\_024671,  
gen.NM\_024671  
Figure 4455: PRO82562  
Figure 4456: DNA326140, NM\_033410,  
gen.NM\_033410  
Figure 4457: PRO82563  
Figure 4458: DNA326141, NM\_024031,  
gen.NM\_024031  
Figure 4459: PRO82564  
Figure 4460A-B: DNA326142, XM\_034375,  
gen.XM\_034375  
Figure 4461: DNA326143, XM\_012569,  
gen.XM\_012569  
Figure 4462: DNA326144, XM\_050194,  
gen.XM\_050194  
Figure 4463: DNA326145, XM\_008106,  
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Figure 4465: DNA326146, NM\_004960,  
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Figure 4466: PRO82568  
Figure 4467: DNA326147, XM\_113293,  
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Figure 4468: DNA326148, NM\_022744,  
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Figure 4469: PRO82570  
Figure 4470: DNA326149, NM\_024048,  
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Figure 4471: PRO82571  
Figure 4472: DNA326150, XM\_018088,  
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Figure 4473: PRO82572  
Figure 4474: DNA326151, XM\_007963,  
gen.XM\_007963  
Figure 4475: PRO82573  
Figure 4476: DNA274002, NM\_014321,  
gen.NM\_014321  
Figure 4477: PRO61948  
Figure 4478: DNA326152, XM\_015700,  
gen.XM\_015700  
Figure 4479: DNA326153, XM\_051219,  
gen.XM\_051219  
Figure 4480: DNA326154, XM\_085393,  
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Figure 4481: PRO82576  
Figure 4482: DNA326155, XM\_085395,  
gen.XM\_085395



Figure 4483: DNA326156, XM\_091270,  
gen.XM\_091270  
Figure 4484: DNA326157, XM\_165656,  
gen.XM\_165656  
Figure 4485: DNA326158, NM\_032330,  
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Figure 4486: PRO82579  
Figure 4487: DNA254532, NM\_001043,  
gen.NM\_001043  
Figure 4488: PRO49639  
Figure 4489: DNA326159, XM\_165658,  
gen.XM\_165658  
Figure 4490: DNA326160, XM\_166285,  
gen.XM\_166285  
Figure 4491: DNA326161, XM\_166282,  
gen.XM\_166282  
Figure 4492: PRO82582  
Figure 4493: DNA326162, XM\_165657,  
gen.XM\_165657  
Figure 4494: PRO82583  
Figure 4495: DNA326163, NM\_032038,  
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Figure 4496: PRO82584  
Figure 4497: DNA326164, XM\_008065,  
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Figure 4498: DNA326165, NM\_017458,  
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Figure 4499: PRO82585  
Figure 4500: DNA326166, NM\_005115,  
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Figure 4501: PRO82586  
Figure 4502: DNA326167, NM\_024516,  
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Figure 4503: PRO82587  
Figure 4504: DNA326168, XM\_113299,  
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Figure 4505: DNA326169, XM\_055771,  
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Figure 4506: PRO82589  
Figure 4507: DNA271171, NM\_007317,  
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Figure 4508: PRO59491  
Figure 4509: DNA326170, XM\_008064,  
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Figure 4510: PRO82590  
Figure 4511: DNA326171, NM\_003123,  
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Figure 4512: PRO2355  
Figure 4513: DNA326172, XM\_085442,  
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Figure 4514: DNA326173, XM\_055132,  
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Figure 4515: PRO82592  
Figure 4516: DNA274180, NM\_007074,  
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Figure 4517: PRO62110

Figure 4518: DNA326174, NM\_002720,  
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Figure 4519: PRO42208  
Figure 4520: DNA287355, NM\_000034,  
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Figure 4521: PRO69617  
Figure 4522: DNA326175, NM\_031478,  
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Figure 4523: PRO82593  
Figure 4524: DNA326176, XM\_085434,  
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Figure 4525: PRO82594  
Figure 4526: DNA326177, XM\_058116,  
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Figure 4527: DNA326178, XM\_165649,  
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Figure 4528: DNA326179, XM\_165647,  
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Figure 4529: PRO82597  
Figure 4530: DNA194805, NM\_014685,  
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Figure 4531: PRO24075  
Figure 4532: DNA326180, XM\_166277,  
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Figure 4533: PRO82598  
Figure 4534: DNA326181, XM\_165645,  
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Figure 4535: DNA326182, NM\_018110,  
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Figure 4536: PRO82599  
Figure 4537: DNA326183, XM\_165648,  
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Figure 4538: DNA326184, XM\_167453,  
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Figure 4539: DNA326185, NM\_022770,  
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Figure 4540: PRO82602  
Figure 4541: DNA326186, XM\_167456,  
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Figure 4542: PRO82603  
Figure 4543: DNA326187, XM\_058745,  
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Figure 4544: DNA326188, XM\_091420,  
gen.XM\_091420  
Figure 4545: DNA326189, NM\_004691,  
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Figure 4546: PRO82606  
Figure 4547: DNA326190, NM\_000196,  
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Figure 4548: PRO82607  
Figure 4549A-B: DNA326191, NM\_004360,  
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Figure 4550: PRO2672  
Figure 4551: DNA326192, XM\_039306,  
gen.XM\_039306  
Figure 4552: PRO82608

Figure 4553: DNA326193, NM\_030579,  
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Figure 4554: PRO82609  
Figure 4555: DNA326194, XM\_012487,  
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Figure 4556: DNA326195, NM\_014062,  
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Figure 4557: PRO82611  
Figure 4558: DNA326196, XM\_085471,  
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Figure 4559: PRO82612  
Figure 4560: DNA326197, XM\_113855,  
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Figure 4561: DNA326198, XM\_085475,  
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Figure 4562: DNA326199, XM\_028151,  
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Figure 4563: PRO82615  
Figure 4564: DNA275408, NM\_001605,  
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Figure 4565: PRO63068  
Figure 4566: DNA326200, NM\_007242,  
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Figure 4567: PRO82616  
Figure 4568: DNA189703, NM\_005548,  
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Figure 4569: PRO22637  
Figure 4570: DNA326201, XM\_113853,  
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Figure 4571: DNA326202, NM\_032140,  
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Figure 4572: PRO82618  
Figure 4573: DNA326203, NM\_030819,  
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Figure 4574: PRO82619  
Figure 4575: DNA304704, NM\_005796,  
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Figure 4576: PRO71130  
Figure 4577: DNA326204, XM\_043047,  
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Figure 4578: PRO49967  
Figure 4579: DNA88261, NM\_001907,  
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Figure 4580: PRO2719  
Figure 4581A-B: DNA326205, NM\_005072,  
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Figure 4582: PRO4814  
Figure 4583: DNA326206, XM\_165410,  
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Figure 4584: DNA326207, NM\_017803,  
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Figure 4585: PRO82621  
Figure 4586A-B: DNA326208, NM\_004555,  
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Figure 4587: PRO82622  
Figure 4588A-B: DNA326209, NM\_018124,

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Figure 4589: PRO82623  
Figure 4590: DNA326210, XM\_091399,  
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Figure 4591: PRO82624  
Figure 4592A-B: DNA326211, NM\_014003,  
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Figure 4593: PRO82625  
Figure 4594: DNA326212, NM\_017853,  
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Figure 4595: PRO82626  
Figure 4596: DNA326213, XM\_042621,  
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Figure 4597: DNA326214, XM\_064091,  
gen.XM\_064091  
Figure 4598: PRO82627  
Figure 4599: DNA326215, XM\_085981,  
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Figure 4600A-B: DNA326216, XM\_051778,  
gen.XM\_051778  
Figure 4601: PRO82629  
Figure 4602: DNA326217, NM\_004483,  
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Figure 4603: PRO82630  
Figure 4604: DNA326218, NM\_020188,  
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Figure 4605: PRO82631  
Figure 4606: DNA326219, XM\_033922,  
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Figure 4607: PRO82632  
Figure 4608: DNA326220, XM\_113840,  
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Figure 4609: PRO82633  
Figure 4610: DNA326221, NM\_016095,  
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Figure 4611: PRO82634  
Figure 4612: DNA326222, NM\_006067,  
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Figure 4613: PRO50658  
Figure 4614: DNA326223, NM\_001861,  
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Figure 4615: PRO82635  
Figure 4616A-B: DNA326224, XM\_085483,  
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Figure 4617: DNA326225, NM\_017566,  
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Figure 4618: PRO82637  
Figure 4619: DNA326226, XM\_057150,  
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Figure 4620: PRO82638  
Figure 4621: DNA326227, XM\_058739,  
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Figure 4622: DNA326228, XM\_085327,  
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Figure 4623: PRO82640  
Figure 4624: DNA326229, XM\_047436,

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Figure 4625: PRO82641  
Figure 4626: DNA227234, NM\_002386,  
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Figure 4627: PRO37697  
Figure 4628: DNA326230, NM\_014972,  
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Figure 4629: PRO82642  
Figure 4630: DNA326231, XM\_071873,  
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Figure 4631: PRO82643  
Figure 4632: DNA326232, XM\_047525,  
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Figure 4633: DNA326233, NM\_000977,  
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Figure 4634: PRO82645  
Figure 4635: DNA326234, NM\_033251,  
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Figure 4636: PRO82646  
Figure 4637: DNA326235, XM\_085408,  
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Figure 4638: DNA326236, NM\_004933,  
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Figure 4639: PRO2198  
Figure 4640: DNA326237, XM\_113882,  
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Figure 4641: DNA326238, XM\_010938,  
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Figure 4642: DNA326239, NM\_006761,  
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Figure 4643: PRO39530  
Figure 4644A-B: DNA326240, XM\_017096,  
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Figure 4645: DNA326241, XM\_033714,  
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Figure 4646A-B: DNA326242, XM\_033689,  
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Figure 4647: DNA326243, NM\_002615,  
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Figure 4648: DNA326244, XM\_056082,  
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Figure 4649: PRO82654  
Figure 4650: DNA326245, XM\_008557,  
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Figure 4651: DNA326246, XM\_045183,  
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Figure 4652: PRO82656  
Figure 4653: DNA326247, XM\_113901,  
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Figure 4654: DNA326248, NM\_080822,  
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Figure 4655: PRO82658  
Figure 4656A-B: DNA326249, XM\_029438,  
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Figure 4657: PRO82659  
Figure 4658: DNA326250, XM\_008509,

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Figure 4659: DNA326251, XM\_085687,  
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Figure 4660: PRO82661  
Figure 4661: DNA326252, XM\_027825,  
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Figure 4662: PRO82662  
Figure 4663: DNA326253, XM\_053717,  
gen.XM\_053717  
Figure 4664: PRO82663  
Figure 4665: DNA326254, NM\_005022,  
gen.NM\_005022  
Figure 4666: PRO62780  
Figure 4667A-B: DNA326255, XM\_028398,  
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Figure 4668: PRO82664  
Figure 4669: DNA326256, NM\_000018,  
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Figure 4670: PRO66265  
Figure 4671: DNA326257, XM\_008334,  
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Figure 4672: DNA326258, NM\_024297,  
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Figure 4673: PRO82665  
Figure 4674: DNA326259, XM\_113324,  
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Figure 4675: DNA326260, XM\_012676,  
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Figure 4676: PRO82667  
Figure 4677: DNA326261, XM\_085691,  
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Figure 4678: DNA326262, XM\_028417,  
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Figure 4679: PRO82669  
Figure 4680A-B: DNA326263, XM\_041964,  
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Figure 4681: PRO82670  
Figure 4682: DNA326264, NM\_019013,  
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Figure 4683: PRO82671  
Figure 4684: DNA326265, XM\_008538,  
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Figure 4685: PRO82672  
Figure 4686: DNA326266, XM\_008441,  
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Figure 4687: DNA97300, NM\_001416,  
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Figure 4688: PRO3647  
Figure 4689: DNA326267, NM\_004870,  
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Figure 4690: PRO82674  
Figure 4691: DNA326268, NM\_006942,  
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Figure 4692: PRO82675  
Figure 4693: DNA326269, XM\_008679,  
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Figure 4694: DNA326270, XM\_008231,  
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Figure 4695: DNA326271, XM\_113328,  
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Figure 4696: DNA326272, XM\_113929,  
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Figure 4697: DNA326273, NM\_001970,  
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Figure 4698: PRO82678  
Figure 4699: DNA297388, NM\_004217,  
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Figure 4700: PRO70812  
Figure 4701: DNA326274, XM\_165421,  
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Figure 4702: PRO82679  
Figure 4703: DNA326275, XM\_113325,  
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Figure 4704: DNA326276, XM\_165422,  
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Figure 4705: PRO49182  
Figure 4706: DNA326277, XM\_113931,  
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Figure 4707: DNA326278, XM\_036659,  
gen.XM\_036659  
Figure 4708: DNA103401, NM\_003876,  
gen.NM\_003876  
Figure 4709: PRO4729  
Figure 4710A-B: DNA326279, XM\_042698,  
gen.XM\_042698  
Figure 4711: PRO82683  
Figure 4712A-B: DNA326280, XM\_017234,  
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Figure 4713: DNA326281, XM\_165418,  
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Figure 4714: DNA304715, NM\_000987,  
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Figure 4715: PRO71141  
Figure 4716A-B: DNA326282, NM\_004618,  
gen.NM\_004618  
Figure 4717: PRO62981  
Figure 4718: DNA326283, XM\_085743,  
gen.XM\_085743  
Figure 4719A-B: DNA254198, NM\_002018,  
gen.NM\_002018  
Figure 4720: PRO49310  
Figure 4721A-B: DNA326284, XM\_039910,  
gen.XM\_039910  
Figure 4722: PRO82687  
Figure 4723A-C: DNA326285, XM\_113310,  
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Figure 4724: DNA326286, XM\_085613,  
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Figure 4725: DNA326287, NM\_006470,  
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Figure 4726: PRO82689  
Figure 4727: DNA326288, XM\_051763,

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Figure 4728: DNA290292, NM\_018955,  
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Figure 4729: PRO70449  
Figure 4730: DNA326289, XM\_058900,  
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Figure 4731: PRO82691  
Figure 4732: DNA326290, XM\_039921,  
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Figure 4733: PRO82692  
Figure 4734: DNA326291, XM\_012549,  
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Figure 4735: DNA326292, XM\_085548,  
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Figure 4736: PRO82694  
Figure 4737: DNA326293, NM\_018019,  
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Figure 4738: PRO82695  
Figure 4739: DNA326294, NM\_138427,  
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Figure 4740: PRO82696  
Figure 4741: DNA326295, XM\_085545,  
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Figure 4742A-B: DNA227084, NM\_004176,  
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Figure 4743: PRO37547  
Figure 4744: DNA326296, XM\_012615,  
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Figure 4745: DNA326297, XM\_085722,  
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Figure 4746: PRO82699  
Figure 4747: DNA255414, NM\_018242,  
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Figure 4748: PRO50481  
Figure 4749: DNA326298, XM\_045044,  
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Figure 4750: DNA326299, XM\_008323,  
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Figure 4751: DNA326300, XM\_045535,  
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Figure 4752A-B: DNA326301, XM\_045551,  
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Figure 4753: PRO82702  
Figure 4754: DNA326302, XM\_097204,  
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Figure 4755: DNA326303, XM\_058867,  
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Figure 4756: PRO82704  
Figure 4757: DNA326304, XM\_085672,  
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Figure 4758: DNA326305, XM\_031536,  
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Figure 4759: PRO82706  
Figure 4760: DNA326306, XM\_008486,  
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Figure 4761: DNA326307, NM\_015584,

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Figure 4762: PRO82707  
Figure 4763: DNA326308, NM\_000638,  
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Figure 4764: PRO82708  
Figure 4765A-B: DNA326309, XM\_031466,  
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Figure 4766: PRO82709  
Figure 4767: DNA326310, XM\_031415,  
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Figure 4768: DNA326311, XM\_117066,  
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Figure 4769: DNA326312, XM\_031427,  
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Figure 4770: PRO82712  
Figure 4771: DNA326313, NM\_032322,  
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Figure 4772: PRO82713  
Figure 4773A-B: DNA326314, XM\_050101,  
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Figure 4774: PRO82714  
Figure 4775: DNA326315, XM\_056730,  
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Figure 4776: PRO82715  
Figure 4777: DNA326316, XM\_008462,  
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Figure 4778: DNA287427, NM\_002815,  
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Figure 4779: PRO69684  
Figure 4780: DNA326317, NM\_015544,  
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Figure 4781: PRO82717  
Figure 4782: DNA188351, NM\_005623,  
gen.NM\_005623  
Figure 4783: PRO21887  
Figure 4784: DNA326318, NM\_002878,  
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Figure 4785: PRO82718  
Figure 4786: DNA326319, NM\_133627,  
gen.NM\_133627  
Figure 4787: PRO82719  
Figure 4788: DNA326320, NM\_133630,  
gen.NM\_133630  
Figure 4789: PRO82720  
Figure 4790: DNA326321, NM\_133629,  
gen.NM\_133629  
Figure 4791: PRO82721  
Figure 4792: DNA326322, NM\_018096,  
gen.NM\_018096  
Figure 4793: PRO37791  
Figure 4794A-B: DNA326323, XM\_039474,  
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Figure 4795: PRO82722  
Figure 4796A-B: DNA66475, NM\_004448,  
gen.NM\_004448  
Figure 4797: PRO1204

Figure 4798: DNA326324, NM\_000981,  
gen.NM\_000981  
Figure 4799: PRO4738  
Figure 4800A-B: DNA326325, XM\_008150,  
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Figure 4801: DNA326326, NM\_000978,  
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Figure 4802: PRO82724  
Figure 4803: DNA326327, XM\_058830,  
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Figure 4804: PRO82725  
Figure 4805: DNA270979, NM\_002809,  
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Figure 4806: PRO59309  
Figure 4807: DNA326328, NM\_000422,  
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Figure 4808: PRO82726  
Figure 4809: DNA326329, XM\_008579,  
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Figure 4810: DNA326330, NM\_002276,  
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Figure 4811: PRO82728  
Figure 4812: DNA272889, NM\_002275,  
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Figure 4813: PRO60979  
Figure 4814: DNA326331, NM\_002274,  
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Figure 4815: PRO82729  
Figure 4816: DNA326332, NM\_000526,  
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Figure 4817: PRO82730  
Figure 4818: DNA326333, XM\_049937,  
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Figure 4819A-B: DNA326334, XM\_113334,  
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Figure 4820: DNA226389, NM\_000964,  
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Figure 4821: PRO36852  
Figure 4822: DNA326335, NM\_006455,  
gen.NM\_006455  
Figure 4823: PRO82732  
Figure 4824: DNA326336, XM\_113938,  
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Figure 4825: DNA326337, XM\_036465,  
gen.XM\_036465  
Figure 4826: DNA326338, XM\_055061,  
gen.XM\_055061  
Figure 4827A-B: DNA326339, XM\_036462,  
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Figure 4828: PRO82736  
Figure 4829: DNA326340, XM\_048654,  
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Figure 4830: DNA326341, NM\_025197,  
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Figure 4831: PRO82737  
Figure 4832: DNA326342, XM\_054038,

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Figure 4833: PRO82738  
Figure 4834: DNA326343, NM\_002265,  
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Figure 4835: PRO82739  
Figure 4836: DNA326344, XM\_032201,  
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Figure 4837: PRO82740  
Figure 4838: DNA326345, NM\_012138,  
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Figure 4839: PRO82741  
Figure 4840: DNA326346, XM\_018534,  
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Figure 4841: DNA227873, NM\_001050,  
gen.NM\_001050  
Figure 4842: PRO38336  
Figure 4843: DNA270975, NM\_000386,  
gen.NM\_000386  
Figure 4844: PRO59305  
Figure 4845: DNA88378, NM\_002087,  
gen.NM\_002087  
Figure 4846: PRO2769  
Figure 4847: DNA326347, NM\_016016,  
gen.NM\_016016  
Figure 4848: PRO82743  
Figure 4849: DNA326348, XM\_012642,  
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Figure 4850A-B: DNA326349, NM\_005474,  
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Figure 4851: PRO82745  
Figure 4852: DNA326350, XM\_045901,  
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Figure 4853: PRO82746  
Figure 4854: DNA257428, NM\_032376,  
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Figure 4855: PRO52010  
Figure 4856: DNA326351, XM\_008351,  
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Figure 4857: DNA326352, XM\_032852,  
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Figure 4858: PRO82748  
Figure 4859: DNA326353, NM\_025233,  
gen.NM\_025233  
Figure 4860: PRO82749  
Figure 4861: DNA326354, XM\_032817,  
gen.XM\_032817  
Figure 4862: PRO82750  
Figure 4863: DNA326355, XM\_032813,  
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Figure 4864: DNA326356, XM\_032766,  
gen.XM\_032766  
Figure 4865: DNA326357, NM\_003766,  
gen.NM\_003766  
Figure 4866: PRO82753  
Figure 4867: DNA326358, XM\_008401,  
gen.XM\_008401

Figure 4868: PRO82754  
Figure 4869: DNA326359, XM\_008402,  
gen.XM\_008402  
Figure 4870: PRO82755  
Figure 4871: DNA326360, NM\_017595,  
gen.NM\_017595  
Figure 4872: PRO82756  
Figure 4873: DNA326361, XM\_085636,  
gen.XM\_085636  
Figure 4874: PRO82757  
Figure 4875: DNA326362, NM\_006373,  
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Figure 4876: PRO82758  
Figure 4877: DNA196642, NM\_005440,  
gen.NM\_005440  
Figure 4878: PRO25115  
Figure 4879A-B: DNA270901, NM\_004247,  
gen.NM\_004247  
Figure 4880: DNA326363, XM\_050159,  
gen.XM\_050159  
Figure 4881: DNA326364, XM\_083983,  
gen.XM\_083983  
Figure 4882: PRO82760  
Figure 4883A-B: DNA326365, NM\_021079,  
gen.NM\_021079  
Figure 4884: PRO82761  
Figure 4885: DNA326366, NM\_133373,  
gen.NM\_133373  
Figure 4886: PRO82762  
Figure 4887: DNA97290, NM\_002512,  
gen.NM\_002512  
Figure 4888: PRO3637  
Figure 4889: DNA227071, NM\_000269,  
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Figure 4890: PRO37534  
Figure 4891: DNA227764, NM\_003971,  
gen.NM\_003971  
Figure 4892: PRO38227  
Figure 4893A-B: DNA326367, NM\_020038,  
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Figure 4894: PRO82763  
Figure 4895A-B: DNA326368, NM\_020037,  
gen.NM\_020037  
Figure 4896: PRO82764  
Figure 4897: DNA326369, XM\_037971,  
gen.XM\_037971  
Figure 4898: DNA254791, NM\_018346,  
gen.NM\_018346  
Figure 4899: PRO49888  
Figure 4900: DNA287425, NM\_018509,  
gen.NM\_018509  
Figure 4901: PRO69682  
Figure 4902A-B: DNA326370, XM\_008432,  
gen.XM\_008432  
Figure 4903: DNA88554, NM\_000250,  
gen.NM\_000250

Figure 4904: PRO2839  
Figure 4905: DNA326371, XM\_113919,  
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Figure 4906: DNA326372, NM\_017777,  
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Figure 4907: PRO82768  
Figure 4908: DNA326373, NM\_006924,  
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Figure 4909: PRO82769  
Figure 4910: DNA326374, XM\_115480,  
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Figure 4911: DNA326375, NM\_005831,  
gen.NM\_005831  
Figure 4912: PRO59328  
Figure 4913: DNA326376, XM\_117061,  
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Figure 4914: PRO82771  
Figure 4915: DNA326377, XM\_008459,  
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Figure 4916A-B: DNA326378, XM\_012651,  
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Figure 4917: DNA326379, NM\_021626,  
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Figure 4918: PRO302  
Figure 4919: DNA287291, NM\_021213,  
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Figure 4920: PRO69561  
Figure 4921A-B: DNA326380, NM\_004859,  
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Figure 4922: PRO82774  
Figure 4923: DNA326381, XM\_083966,  
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Figure 4924: DNA326382, XM\_044426,  
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Figure 4925: PRO82776  
Figure 4926: DNA326383, XM\_008253,  
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Figure 4927: DNA326384, XM\_044394,  
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Figure 4928: PRO10400  
Figure 4929: DNA326385, NM\_017647,  
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Figure 4930: PRO82778  
Figure 4931: DNA326386, NM\_007372,  
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Figure 4932: PRO82779  
Figure 4933: DNA326387, NM\_002401,  
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Figure 4934: PRO37764  
Figure 4935: DNA326388, XM\_044376,  
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Figure 4936A-B: DNA150457, NM\_006039,  
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Figure 4937: PRO12265  
Figure 4938: DNA326389, XM\_044367,  
gen.XM\_044367

Figure 4939: DNA227055, NM\_002634,  
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Figure 4940: PRO37518  
Figure 4941: DNA326390, XM\_011118,  
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Figure 4942: DNA326391, XM\_055199,  
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Figure 4943A-B: DNA326392, XM\_044372,  
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Figure 4944: DNA326393, XM\_113315,  
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Figure 4945: DNA326394, XM\_012609,  
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Figure 4946: DNA326395, NM\_005220,  
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Figure 4947: PRO82787  
Figure 4948: DNA326396, XM\_085589,  
gen.XM\_085589  
Figure 4949: PRO82788  
Figure 4950: DNA326397, XM\_012634,  
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Figure 4951: DNA326398, XM\_085627,  
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Figure 4952: PRO82790  
Figure 4953: DNA150814, NM\_002086,  
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Figure 4954: PRO12806  
Figure 4955: DNA326399, NM\_024844,  
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Figure 4956: PRO82791  
Figure 4957: DNA326400, XM\_041583,  
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Figure 4958: DNA326401, XM\_046932,  
gen.XM\_046932  
Figure 4959: PRO82792  
Figure 4960: DNA326402, NM\_004524,  
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Figure 4961: PRO82793  
Figure 4962A-B: DNA326403, XM\_113951,  
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Figure 4963A-B: DNA88430, NM\_000213,  
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Figure 4964: PRO2788  
Figure 4965A-B: DNA326404, XM\_036104,  
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Figure 4966: PRO82794  
Figure 4967: DNA326405, NM\_000154,  
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Figure 4968: PRO82795  
Figure 4969: DNA326406, NM\_005324,  
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Figure 4970: PRO11403  
Figure 4971A-B: DNA326407, XM\_036115,  
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Figure 4972: PRO82796  
Figure 4973: DNA326408, XM\_054344,

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Figure 4974: PRO82797  
Figure 4975: DNA274755, NM\_002766,  
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Figure 4976: PRO70703  
Figure 4977A-B: DNA326409, XM\_085531,  
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Figure 4978: DNA326410, XM\_113892,  
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Figure 4979: PRO82799  
Figure 4980: DNA326411, XM\_017578,  
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Figure 4981: PRO82800  
Figure 4982: DNA326412, XM\_036785,  
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Figure 4983: PRO39201  
Figure 4984: DNA326413, XM\_097043,  
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Figure 4985: DNA129504, NM\_001168,  
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Figure 4986: PRO7143  
Figure 4987: DNA326414, XM\_037196,  
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Figure 4988: DNA326415, XM\_037195,  
gen.XM\_037195  
Figure 4989: DNA326416, XM\_045104,  
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Figure 4990: PRO37540  
Figure 4991: DNA326417, XM\_085563,  
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Figure 4992A-B: DNA326418, XM\_085716,  
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Figure 4993: PRO82805  
Figure 4994A-B: DNA326419, XM\_049934,  
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Figure 4995: DNA326420, XM\_049931,  
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Figure 4996A-B: DNA326421, XM\_045581,  
gen.XM\_045581  
Figure 4997: PRO82807  
Figure 4998: DNA326422, XM\_113945,  
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Figure 4999: DNA326423, XM\_046481,  
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Figure 5000: DNA326424, XM\_097195,  
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Figure 5001: DNA326425, XM\_097193,  
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Figure 5002: DNA326426, NM\_004309,  
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Figure 5003: PRO61246  
Figure 5004: DNA326427, XM\_046472,  
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Figure 5005: PRO82812  
Figure 5006: DNA326428, NM\_016286,  
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Figure 5007: PRO82813  
Figure 5008: DNA326429, NM\_004127,  
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Figure 5009: PRO82814  
Figure 5010A-C: DNA326430, XM\_113943,  
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Figure 5011: DNA326431, XM\_113330,  
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Figure 5012: PRO82816  
Figure 5013: DNA326432, XM\_113303,  
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Figure 5014: DNA287234, NM\_031968,  
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Figure 5015: PRO69513  
Figure 5016: DNA326433, NM\_022158,  
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Figure 5017: PRO82818  
Figure 5018: DNA326434, XM\_038424,  
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Figure 5019: DNA326435, XM\_085735,  
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Figure 5020: DNA326436, XM\_046765,  
gen.XM\_046765  
Figure 5021: DNA326437, XM\_046769,  
gen.XM\_046769  
Figure 5022: DNA326438, XM\_046767,  
gen.XM\_046767  
Figure 5023: DNA273694, NM\_006101,  
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Figure 5024: PRO61661  
Figure 5025A-B: DNA326439, XM\_028744,  
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Figure 5026: DNA326440, XM\_165954,  
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Figure 5027: DNA326441, XM\_041678,  
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Figure 5028: DNA326442, XM\_113343,  
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Figure 5029: PRO82825  
Figure 5030: DNA326443, XM\_067325,  
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Figure 5031: DNA326444, XM\_012741,  
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Figure 5032: DNA326445, NM\_014214,  
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Figure 5033: PRO82828  
Figure 5034A-B: DNA326446, XM\_035640,  
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Figure 5035: PRO82829  
Figure 5036: DNA326447, XM\_016382,  
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Figure 5037: DNA326448, NM\_032933,  
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Figure 5038: PRO82831  
Figure 5039: DNA274690, NM\_006938,  
gen.NM\_006938



Figure 5040A-B: DNA88457, NM\_000227,  
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Figure 5041: PRO2799  
Figure 5042: DNA326449, XM\_085791,  
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Figure 5043: DNA326450, XM\_085789,  
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Figure 5044: PRO82833  
Figure 5045: DNA326451, XM\_085790,  
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Figure 5046: DNA326452, XM\_015755,  
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Figure 5047: PRO82835  
Figure 5048: DNA326453, XM\_097232,  
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Figure 5049: DNA326454, XM\_085788,  
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Figure 5050: DNA88281, NM\_001944,  
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Figure 5051: PRO2267  
Figure 5052: DNA271841, NM\_003787,  
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Figure 5053: PRO60121  
Figure 5054: DNA326455, XM\_008723,  
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Figure 5055: DNA326456, XM\_084007,  
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Figure 5056: DNA256813, NM\_018255,  
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Figure 5057: PRO51744  
Figure 5058: DNA326457, XM\_085775,  
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Figure 5059: PRO82840  
Figure 5060: DNA326458, NM\_138443,  
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Figure 5061: PRO82841  
Figure 5062: DNA326459, XM\_038872,  
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Figure 5063: PRO82842  
Figure 5064: DNA326460, XM\_086779,  
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Figure 5065: DNA326461, XM\_167363,  
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Figure 5066: DNA326462, XM\_031944,  
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Figure 5067: DNA326463, NM\_000985,  
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Figure 5068: PRO82846  
Figure 5069: DNA326464, NM\_002396,  
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Figure 5070: PRO61113  
Figure 5071: DNA326465, XM\_166288,  
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Figure 5072: DNA326466, NM\_004539,  
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Figure 5073: PRO60800

Figure 5074: DNA326467, XM\_006937,  
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Figure 5075: DNA326468, XM\_085779,  
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Figure 5076: DNA326469, XM\_011089,  
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Figure 5077: PRO82850  
Figure 5078: DNA326470, XM\_169540,  
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Figure 5079: PRO82851  
Figure 5080: DNA326471, XM\_167008,  
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Figure 5081: PRO82852  
Figure 5082: DNA326472, XM\_048471,  
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Figure 5083A-B: DNA326473, XM\_008812,  
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Figure 5084A-B: DNA326474, XM\_117096,  
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Figure 5085: PRO82855  
Figure 5086: DNA326475, NM\_002385,  
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Figure 5087: PRO82856  
Figure 5088: DNA326476, XM\_015241,  
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Figure 5089A-B: DNA326477, XM\_008695,  
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Figure 5090A-B: DNA326478, XM\_041872,  
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Figure 5091: PRO82859  
Figure 5092: DNA326479, XM\_051586,  
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Figure 5093: DNA326480, NM\_003712,  
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Figure 5094: PRO1077  
Figure 5095: DNA326481, XM\_042018,  
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Figure 5096: PRO2560  
Figure 5097: DNA326482, XM\_114018,  
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Figure 5098: DNA326483, NM\_017876,  
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Figure 5099: PRO82861  
Figure 5100: DNA326484, NM\_031990,  
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Figure 5101: PRO82862  
Figure 5102: DNA326485, NM\_002819,  
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Figure 5103: PRO62899  
Figure 5104: DNA326486, NM\_005224,  
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Figure 5105: PRO82863  
Figure 5106: DNA326487, XM\_037565,  
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Figure 5107: PRO82864  
Figure 5108: DNA326488, XM\_092042,

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 Figure 5109: DNA326489, XM\_037572,  
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 Figure 5110: DNA326490, XM\_009279,  
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 Figure 5111: PRO82867  
 Figure 5112: DNA326491, NM\_002085,  
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 Figure 5113A-B: DNA326492, XM\_009277,  
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 Figure 5114: DNA326493, XM\_012913,  
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 Figure 5115: DNA274101, NM\_001687,  
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 Figure 5116: PRO62039  
 Figure 5117: DNA326494, XM\_028067,  
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 Figure 5118: PRO82871  
 Figure 5119: DNA326495, XM\_028064,  
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 Figure 5120: DNA326496, NM\_024407,  
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 Figure 5121: PRO82872  
 Figure 5122: DNA326497, NM\_000156,  
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 Figure 5123: PRO58046  
 Figure 5124: DNA326498, NM\_138924,  
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 Figure 5125: PRO82873  
 Figure 5126: DNA326499, NM\_001018,  
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 Figure 5127: PRO10485  
 Figure 5128: DNA326500, XM\_086101,  
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 Figure 5129: PRO82874  
 Figure 5130: DNA326501, XM\_086102,  
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 Figure 5131: DNA326502, XM\_047584,  
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 Figure 5132A-B: DNA326503, XM\_047600,  
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 Figure 5133: PRO38496  
 Figure 5134: DNA326504, XM\_097420,  
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 Figure 5135A-B: DNA326505, XM\_030721,  
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 Figure 5136: PRO82877  
 Figure 5137: DNA326506, XM\_030720,  
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 Figure 5138: DNA326507, NM\_031213,  
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 Figure 5139: PRO82879  
 Figure 5140: DNA326508, XM\_039723,  
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 Figure 5141: DNA326509, NM\_001319,  
 gen.NM\_001319

Figure 5142: PRO82881  
 Figure 5143: DNA326510, NM\_017797,  
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 Figure 5144: PRO82882  
 Figure 5145: DNA326511, XM\_030714,  
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 Figure 5146: DNA256555, NM\_017572,  
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 Figure 5147: PRO51586  
 Figure 5148A-B: DNA326512, NM\_003938,  
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 Figure 5149: PRO82884  
 Figure 5150A-B: DNA326513, XM\_046822,  
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 Figure 5151: PRO82885  
 Figure 5152: DNA326514, NM\_007165,  
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 Figure 5153: PRO82886  
 Figure 5154: DNA287636, NM\_004152,  
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 Figure 5155: DNA326515, NM\_012458,  
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 Figure 5157: DNA326516, NM\_032737,  
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 Figure 5158: PRO82888  
 Figure 5159: DNA326517, XM\_030485,  
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 Figure 5160: DNA326518, XM\_046934,  
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 Figure 5161: DNA326519, NM\_003021,  
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 Figure 5162: PRO62302  
 Figure 5163: DNA326520, XM\_055686,  
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 Figure 5164: PRO37951  
 Figure 5165: DNA326521, XM\_009222,  
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 Figure 5166: DNA326522, XM\_052635,  
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 Figure 5167: PRO82892  
 Figure 5168: DNA326523, XM\_052661,  
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 Figure 5169: DNA326524, NM\_016263,  
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 Figure 5170: PRO82893  
 Figure 5171: DNA326525, NM\_006339,  
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 Figure 5172: PRO82894  
 Figure 5173: DNA326526, NM\_032753,  
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 Figure 5174: PRO82895  
 Figure 5175: DNA326527, XM\_056421,  
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 Figure 5176A-B: DNA326528, XM\_031917,  
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Figure 5177: PRO82897  
 Figure 5178: DNA326529, NM\_001961,  
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 Figure 5179: PRO62225  
 Figure 5180: DNA326530, XM\_016871,  
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 Figure 5181: DNA326531, NM\_016539,  
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 Figure 5182: PRO82899  
 Figure 5183: DNA326532, XM\_117122,  
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 Figure 5184: DNA326533, XM\_031857,  
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 Figure 5185: PRO82901  
 Figure 5186: DNA326534, NM\_024333,  
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 Figure 5187: PRO82902  
 Figure 5188: DNA326535, NM\_003025,  
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 Figure 5189: PRO82903  
 Figure 5190: DNA326536, NM\_025241,  
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 Figure 5191: PRO82904  
 Figure 5192: DNA326537, XM\_035638,  
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 Figure 5193: PRO82905  
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 Figure 5195: DNA326539, XM\_012862,  
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 Figure 5196A-B: DNA326540, XM\_035627,  
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 Figure 5197A-B: DNA326541, XM\_035625,  
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 Figure 5198: PRO82909  
 Figure 5199: DNA274761, NM\_014649,  
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 Figure 5200: PRO62531  
 Figure 5201: DNA272421, NM\_006012,  
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 Figure 5202: PRO60674  
 Figure 5203: DNA326542, NM\_003685,  
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 Figure 5204: PRO82910  
 Figure 5205A-B: DNA326543, XM\_009010,  
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 Figure 5206: DNA270315, NM\_004240,  
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 Figure 5207: PRO58702  
 Figure 5208: DNA326544, NM\_005490,  
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 Figure 5209: PRO201  
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 Figure 5211: PRO82912  
 Figure 5212: DNA326547, XM\_012798,

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 Figure 5215: PRO82915  
 Figure 5216: DNA326550, NM\_016579,  
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 Figure 5217: PRO224  
 Figure 5218A-B: DNA326551, XM\_048351,  
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 Figure 5219: DNA326552, XM\_048364,  
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 Figure 5220: PRO82917  
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 Figure 5222: DNA326554, XM\_097300,  
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 Figure 5223: DNA326555, XM\_049282,  
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 Figure 5224: PRO82920  
 Figure 5225: DNA326556, XM\_058232,  
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 Figure 5226: DNA326557, XM\_045151,  
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 Figure 5227A-B: DNA326558, XM\_050435,  
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 Figure 5228: PRO82923  
 Figure 5229: DNA326559, XM\_113988,  
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 Figure 5230: DNA326560, NM\_058164,  
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 Figure 5231: PRO82925  
 Figure 5232: DNA227280, NM\_020230,  
 gen.NM\_020230  
 Figure 5233: PRO37743  
 Figure 5234: DNA270621, NM\_003755,  
 gen.NM\_003755  
 Figure 5235: PRO58991  
 Figure 5236: DNA326561, XM\_049502,  
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 Figure 5237: DNA326562, NM\_007065,  
 gen.NM\_007065  
 Figure 5238: PRO63226  
 Figure 5239: DNA326563, XM\_049561,  
 gen.XM\_049561  
 Figure 5240: DNA326564, XM\_017204,  
 gen.XM\_017204  
 Figure 5241: DNA326565, NM\_005498,  
 gen.NM\_005498  
 Figure 5242: PRO62112  
 Figure 5243: DNA326566, XM\_008887,  
 gen.XM\_008887  
 Figure 5244: DNA326567, XM\_085862,  
 gen.XM\_085862  
 Figure 5245: PRO82930

Figure 5246: DNA326568, XM\_084014,  
gen.XM\_084014  
Figure 5247A-B: DNA326569, XM\_032710,  
gen.XM\_032710  
Figure 5248: DNA326570, XM\_032719,  
gen.XM\_032719  
Figure 5249: PRO82933  
Figure 5250: DNA326571, NM\_024029,  
gen.NM\_024029  
Figure 5251: PRO23794  
Figure 5252: DNA326572, XM\_032724,  
gen.XM\_032724  
Figure 5253: PRO82934  
Figure 5254A-B: DNA326573, NM\_003072,  
gen.NM\_003072  
Figure 5255: PRO82935  
Figure 5256A-B: DNA326574, XM\_009082,  
gen.XM\_009082  
Figure 5257: DNA326575, XM\_032774,  
gen.XM\_032774  
Figure 5258: DNA218271, NM\_000121,  
gen.NM\_000121  
Figure 5259: PRO34323  
Figure 5260: DNA326576, XM\_057074,  
gen.XM\_057074  
Figure 5261: DNA326577, XM\_032782,  
gen.XM\_032782  
Figure 5262: DNA326578, NM\_032377,  
gen.NM\_032377  
Figure 5263: PRO82939  
Figure 5264: DNA326579, XM\_015697,  
gen.XM\_015697  
Figure 5265: PRO82940  
Figure 5266: DNA326580, XM\_010156,  
gen.XM\_010156  
Figure 5267: DNA326581, NM\_001930,  
gen.NM\_001930  
Figure 5268: PRO58446  
Figure 5269: DNA326582, NM\_013406,  
gen.NM\_013406  
Figure 5270: DNA326583, NM\_013407,  
gen.NM\_013407  
Figure 5271: PRO82943  
Figure 5272: DNA103320, NM\_002229,  
gen.NM\_002229  
Figure 5273: PRO4650  
Figure 5274: DNA326584, XM\_009063,  
gen.XM\_009063  
Figure 5275: PRO82944  
Figure 5276: DNA326585, XM\_085917,  
gen.XM\_085917  
Figure 5277: DNA274034, NM\_006397,  
gen.NM\_006397  
Figure 5278: PRO61977  
Figure 5279: DNA287243, NM\_004461,  
gen.NM\_004461

Figure 5280: PRO69518  
Figure 5281: DNA326586, XM\_032020,  
gen.XM\_032020  
Figure 5282: PRO2718  
Figure 5283: DNA326587, NM\_005053,  
gen.NM\_005053  
Figure 5284: PRO22613  
Figure 5285: DNA326588, XM\_085916,  
gen.XM\_085916  
Figure 5286: DNA326589, NM\_017722,  
gen.NM\_017722  
Figure 5287: PRO82947  
Figure 5288: DNA326590, NM\_003765,  
gen.NM\_003765  
Figure 5289: PRO82948  
Figure 5290: DNA326591, XM\_051364,  
gen.XM\_051364  
Figure 5291: PRO82949  
Figure 5292: DNA326592, XM\_031345,  
gen.XM\_031345  
Figure 5293: PRO82950  
Figure 5294: DNA326593, XM\_113352,  
gen.XM\_113352  
Figure 5295: DNA326594, XM\_058967,  
gen.XM\_058967  
Figure 5296: PRO82952  
Figure 5297: DNA326595, XM\_085909,  
gen.XM\_085909  
Figure 5298: DNA269894, NM\_002730,  
gen.NM\_002730  
Figure 5299: PRO58292  
Figure 5300: DNA326596, NM\_018154,  
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Figure 5301: PRO82954  
Figure 5302: DNA326597, XM\_031276,  
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Figure 5303: DNA326598, XM\_031273,  
gen.XM\_031273  
Figure 5304: PRO82956  
Figure 5305: DNA326599, XM\_031263,  
gen.XM\_031263  
Figure 5306: PRO82957  
Figure 5307: DNA326600, XM\_031251,  
gen.XM\_031251  
Figure 5308: DNA326601, NM\_006844,  
gen.NM\_006844  
Figure 5309: PRO82958  
Figure 5310A-C: DNA326602, XM\_009303,  
gen.XM\_009303  
Figure 5311: DNA326603, XM\_086074,  
gen.XM\_086074  
Figure 5312: DNA269630, NM\_003290,  
gen.NM\_003290  
Figure 5313: PRO58042  
Figure 5314: DNA326604, NM\_005370,  
gen.NM\_005370

Figure 5315: PRO12130  
Figure 5316: DNA326605, XM\_113348,  
gen.XM\_113348  
Figure 5317: DNA326606, NM\_032207,  
gen.NM\_032207  
Figure 5318: PRO82962  
Figure 5319A-B: DNA326607, NM\_006387,  
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Figure 5320: PRO82963  
Figure 5321: DNA326608, NM\_024881,  
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Figure 5322: PRO82964  
Figure 5323: DNA326609, NM\_024104,  
gen.NM\_024104  
Figure 5324: PRO82965  
Figure 5325A-C: DNA326610, XM\_008854,  
gen.XM\_008854  
Figure 5326: DNA326611, NM\_014173,  
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Figure 5327: PRO82967  
Figure 5328: DNA287240, NM\_004335,  
gen.NM\_004335  
Figure 5329: PRO29371  
Figure 5330: DNA326612, XM\_050660,  
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Figure 5331: DNA326613, XM\_086116,  
gen.XM\_086116  
Figure 5332: DNA326614, NM\_018174,  
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Figure 5333: PRO82970  
Figure 5334: DNA326615, NM\_000980,  
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Figure 5335: PRO82971  
Figure 5336: DNA326616, XM\_055230,  
gen.XM\_055230  
Figure 5337: DNA326617, XM\_012179,  
gen.XM\_012179  
Figure 5338A-B: DNA326618, XM\_009293,  
gen.XM\_009293  
Figure 5339: DNA326619, XM\_038146,  
gen.XM\_038146  
Figure 5340: PRO82975  
Figure 5341: DNA326620, XM\_092046,  
gen.XM\_092046  
Figure 5342: PRO82976  
Figure 5343: DNA326621, XM\_038098,  
gen.XM\_038098  
Figure 5344: PRO82977  
Figure 5345: DNA326622, NM\_032627,  
gen.NM\_032627  
Figure 5346: PRO82978  
Figure 5347: DNA326623, XM\_165960,  
gen.XM\_165960  
Figure 5348: PRO82979  
Figure 5349: DNA326624, XM\_114004,  
gen.XM\_114004

Figure 5350: DNA326625, NM\_012181,  
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Figure 5351: PRO82980  
Figure 5352: DNA227249, NM\_007263,  
gen.NM\_007263  
Figure 5353: PRO37712  
Figure 5354: DNA326626, XM\_018515,  
gen.XM\_018515  
Figure 5355: DNA326627, NM\_033415,  
gen.NM\_033415  
Figure 5356: PRO82982  
Figure 5357: DNA326628, XM\_009330,  
gen.XM\_009330  
Figure 5358: DNA326629, NM\_134440,  
gen.NM\_134440  
Figure 5359: PRO82983  
Figure 5360: DNA326630, NM\_003721,  
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Figure 5361: PRO59220  
Figure 5362: DNA326631, NM\_015965,  
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Figure 5363: PRO82984  
Figure 5364: DNA326632, XM\_016378,  
gen.XM\_016378  
Figure 5365: PRO82985  
Figure 5366: DNA326633, XM\_114027,  
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Figure 5367: DNA326634, XM\_165963,  
gen.XM\_165963  
Figure 5368: PRO82987  
Figure 5369: DNA326635, XM\_015769,  
gen.XM\_015769  
Figure 5370: DNA326636, XM\_012812,  
gen.XM\_012812  
Figure 5371: DNA326637, XM\_085971,  
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Figure 5372: DNA326638, XM\_037662,  
gen.XM\_037662  
Figure 5373: PRO82991  
Figure 5374: DNA326639, NM\_001238,  
gen.NM\_001238  
Figure 5375: PRO82992  
Figure 5376: DNA326640, NM\_057182,  
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Figure 5377: PRO4756  
Figure 5378: DNA326641, XM\_009180,  
gen.XM\_009180  
Figure 5379: DNA326642, XM\_117118,  
gen.XM\_117118  
Figure 5380: DNA326643, XM\_092049,  
gen.XM\_092049  
Figure 5381: PRO82995  
Figure 5382: DNA326644, XM\_028672,  
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Figure 5383: DNA326645, XM\_028666,  
gen.XM\_028666

Figure 5384: DNA326646, XM\_009338,  
gen.XM\_009338  
Figure 5385: DNA326647, XM\_048258,  
gen.XM\_048258  
Figure 5386: PRO82998  
Figure 5387: DNA256836, NM\_018468,  
gen.NM\_018468  
Figure 5388: PRO51767  
Figure 5389: DNA326648, NM\_024321,  
gen.NM\_024321  
Figure 5390: PRO82999  
Figure 5391A-B: DNA326649, XM\_049237,  
gen.XM\_049237  
Figure 5392: PRO83000  
Figure 5393: DNA326650, NM\_032635,  
gen.NM\_032635  
Figure 5394: PRO23845  
Figure 5395: DNA326651, XM\_115615,  
gen.XM\_115615  
Figure 5396A-B: DNA326652, XM\_091984,  
gen.XM\_091984  
Figure 5397: PRO83002  
Figure 5398: DNA326653, XM\_085986,  
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Figure 5399: DNA326654, XM\_032285,  
gen.XM\_032285  
Figure 5400: PRO83004  
Figure 5401: DNA326655, NM\_002812,  
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Figure 5402: PRO83005  
Figure 5403A-E: DNA326656, XM\_029455,  
gen.XM\_029455  
Figure 5404: DNA326657, XM\_029450,  
gen.XM\_029450  
Figure 5405: PRO83007  
Figure 5406: DNA326658, XM\_009149,  
gen.XM\_009149  
Figure 5407: PRO62500  
Figure 5408: DNA326659, XM\_056602,  
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Figure 5409: DNA326660, NM\_012237,  
gen.NM\_012237  
Figure 5410: PRO83008  
Figure 5411: DNA326661, NM\_030593,  
gen.NM\_030593  
Figure 5412: PRO83009  
Figure 5413: DNA326662, NM\_017827,  
gen.NM\_017827  
Figure 5414: PRO83010  
Figure 5415: DNA326663, NM\_021107,  
gen.NM\_021107  
Figure 5416: PRO83011  
Figure 5417: DNA326664, NM\_033363,  
gen.NM\_033363  
Figure 5418: PRO83012  
Figure 5419: DNA326665, XM\_059045,

gen.XM\_059045  
Figure 5420: PRO83013  
Figure 5421: DNA273474, NM\_005884,  
gen.NM\_005884  
Figure 5422: PRO61458  
Figure 5423: DNA326666, XM\_046090,  
gen.XM\_046090  
Figure 5424: PRO83014  
Figure 5425: DNA326667, XM\_086004,  
gen.XM\_086004  
Figure 5426: DNA272347, NM\_001020,  
gen.NM\_001020  
Figure 5427: PRO60603  
Figure 5428A-B: DNA326668, NM\_003169,  
gen.NM\_003169  
Figure 5429: PRO12822  
Figure 5430: DNA326669, XM\_053074,  
gen.XM\_053074  
Figure 5431: PRO83016  
Figure 5432: DNA326670, NM\_016941,  
gen.NM\_016941  
Figure 5433: PRO83017  
Figure 5434: DNA256840, NM\_004714,  
gen.NM\_004714  
Figure 5435: PRO51771  
Figure 5436: DNA326671, NM\_001436,  
gen.NM\_001436  
Figure 5437: PRO83018  
Figure 5438: DNA326672, XM\_016410,  
gen.XM\_016410  
Figure 5439: DNA326673, XM\_012860,  
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Figure 5440: DNA326674, XM\_097365,  
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Figure 5441: DNA274139, NM\_006503,  
gen.NM\_006503  
Figure 5442: PRO62075  
Figure 5443: DNA326675, XM\_009203,  
gen.XM\_009203  
Figure 5444: DNA326676, XM\_047409,  
gen.XM\_047409  
Figure 5445: DNA326677, XM\_047376,  
gen.XM\_047376  
Figure 5446A-B: DNA326678, XM\_047374,  
gen.XM\_047374  
Figure 5447: DNA326679, XM\_059052,  
gen.XM\_059052  
Figure 5448: DNA273600, NM\_004596,  
gen.NM\_004596  
Figure 5449: PRO61575  
Figure 5450: DNA326680, XM\_030914,  
gen.XM\_030914  
Figure 5451: DNA326681, NM\_052848,  
gen.NM\_052848  
Figure 5452: PRO83027  
Figure 5453: DNA326682, XM\_008912,

gen.XM\_008912  
Figure 5454: DNA326683, NM\_020158,  
gen.NM\_020158  
Figure 5455: PRO83029  
Figure 5456: DNA326684, XM\_030901,  
gen.XM\_030901  
Figure 5457: PRO83030  
Figure 5458: DNA326685, NM\_018035,  
gen.NM\_018035  
Figure 5459: PRO83031  
Figure 5460: DNA326686, XM\_085874,  
gen.XM\_085874  
Figure 5461: DNA326687, XM\_085875,  
gen.XM\_085875  
Figure 5462: DNA326688, XM\_085876,  
gen.XM\_085876  
Figure 5463: DNA326689, XM\_058949,  
gen.XM\_058949  
Figure 5464: PRO83035  
Figure 5465: DNA326690, XM\_030895,  
gen.XM\_030895  
Figure 5466: DNA326691, XM\_115603,  
gen.XM\_115603  
Figure 5467: PRO83037  
Figure 5468: DNA326692, NM\_001022,  
gen.NM\_001022  
Figure 5469: PRO83038  
Figure 5470: DNA326693, NM\_004706,  
gen.NM\_004706  
Figure 5471: PRO83039  
Figure 5472: DNA326694, XM\_008878,  
gen.XM\_008878  
Figure 5473: PRO83040  
Figure 5474: DNA326695, NM\_022752,  
gen.NM\_022752  
Figure 5475: PRO83041  
Figure 5476: DNA151808, NM\_006494,  
gen.NM\_006494  
Figure 5477: PRO12892  
Figure 5478: DNA326696, NM\_001816,  
gen.NM\_001816  
Figure 5479: PRO34151  
Figure 5480: DNA326697, NM\_000554,  
gen.NM\_000554  
Figure 5481: PRO83042  
Figure 5482: DNA326698, XM\_049920,  
gen.XM\_049920  
Figure 5483: DNA326699, XM\_055859,  
gen.XM\_055859  
Figure 5484A-B: DNA326700, XM\_009125,  
gen.XM\_009125  
Figure 5485: DNA326701, XM\_008860,  
gen.XM\_008860  
Figure 5486: DNA326702, XM\_009036,  
gen.XM\_009036  
Figure 5487: DNA326703, XM\_085950,

gen.XM\_085950  
Figure 5488: DNA326704, XM\_028263,  
gen.XM\_028263  
Figure 5489: DNA326705, XM\_085928,  
gen.XM\_085928  
Figure 5490: PRO36963  
Figure 5491: DNA326706, XM\_028267,  
gen.XM\_028267  
Figure 5492: DNA326707, NM\_013403,  
gen.NM\_013403  
Figure 5493: PRO83050  
Figure 5494: DNA103580, NM\_001743,  
gen.NM\_001743  
Figure 5495: PRO4904  
Figure 5496: DNA326708, XM\_009126,  
gen.XM\_009126  
Figure 5497: DNA326709, NM\_006247,  
gen.NM\_006247  
Figure 5498: PRO25881  
Figure 5499: DNA326710, NM\_003370,  
gen.NM\_003370  
Figure 5500: PRO83052  
Figure 5501: DNA326711, XM\_085856,  
gen.XM\_085856  
Figure 5502: DNA150784, NM\_001983,  
gen.NM\_001983  
Figure 5503: PRO12800  
Figure 5504: DNA270931, NM\_012099,  
gen.NM\_012099  
Figure 5505: PRO59264  
Figure 5506A-B: DNA257531, NM\_031417,  
gen.NM\_031417  
Figure 5507: PRO52101  
Figure 5508: DNA326712, NM\_001294,  
gen.NM\_001294  
Figure 5509: PRO83054  
Figure 5510: DNA326713, XM\_097274,  
gen.XM\_097274  
Figure 5511: DNA88084, NM\_000041,  
gen.NM\_000041  
Figure 5512: PRO2644  
Figure 5513: DNA256533, NM\_006114,  
gen.NM\_006114  
Figure 5514: PRO51565  
Figure 5515: DNA251057, NM\_002856,  
gen.NM\_002856  
Figure 5516: PRO47354  
Figure 5517: DNA226011, NM\_005581,  
gen.NM\_005581  
Figure 5518: PRO36474  
Figure 5519: DNA326714, NM\_012116,  
gen.NM\_012116  
Figure 5520: PRO83056  
Figure 5521: DNA326715, XM\_097275,  
gen.XM\_097275  
Figure 5522: DNA326716, XM\_008851,

gen.XM\_008851  
Figure 5523: DNA274289, NM\_016440,  
gen.NM\_016440  
Figure 5524: PRO62212  
Figure 5525: DNA326717, NM\_012068,  
gen.NM\_012068  
Figure 5526: PRO83059  
Figure 5527: DNA326718, XM\_085927,  
gen.XM\_085927  
Figure 5528: DNA326719, XM\_084023,  
gen.XM\_084023  
Figure 5529: DNA326720, XM\_167530,  
gen.XM\_167530  
Figure 5530: DNA326721, XM\_114025,  
gen.XM\_114025  
Figure 5531: DNA326722, XM\_008985,  
gen.XM\_008985  
Figure 5532: DNA326723, NM\_030973,  
gen.NM\_030973  
Figure 5533: PRO83065  
Figure 5534: DNA326724, NM\_025129,  
gen.NM\_025129  
Figure 5535: PRO83066  
Figure 5536: DNA326725, NM\_014203,  
gen.NM\_014203  
Figure 5537: DNA326726, XM\_085934,  
gen.XM\_085934  
Figure 5538: PRO83068  
Figure 5539: DNA326727, NM\_001536,  
gen.NM\_001536  
Figure 5540: PRO83069  
Figure 5541: DNA326728, XM\_165432,  
gen.XM\_165432  
Figure 5542: DNA274823, NM\_001571,  
gen.NM\_001571  
Figure 5543: PRO62582  
Figure 5544A-B: DNA326729, XM\_046313,  
gen.XM\_046313  
Figure 5545: PRO83071  
Figure 5546: DNA326730, NM\_015953,  
gen.NM\_015953  
Figure 5547: PRO83072  
Figure 5548: DNA326731, XM\_027904,  
gen.XM\_027904  
Figure 5549: DNA326732, XM\_084026,  
gen.XM\_084026  
Figure 5550: DNA290260, NM\_012423,  
gen.NM\_012423  
Figure 5551: PRO70385  
Figure 5552: DNA326733, XM\_058991,  
gen.XM\_058991  
Figure 5553: PRO83073  
Figure 5554: DNA326734, NM\_017916,  
gen.NM\_017916  
Figure 5555: PRO83074  
Figure 5556: DNA326735, NM\_003598,

gen.NM\_003598  
Figure 5557: PRO83075  
Figure 5558: DNA326736, NM\_006666,  
gen.NM\_006666  
Figure 5559: PRO83076  
Figure 5560: DNA326737, XM\_114024,  
gen.XM\_114024  
Figure 5561: PRO83077  
Figure 5562: DNA304658, NM\_000146,  
gen.NM\_000146  
Figure 5563: PRO71085  
Figure 5564: DNA326738, NM\_004324,  
gen.NM\_004324  
Figure 5565: PRO38101  
Figure 5566: DNA326739, NM\_006184,  
gen.NM\_006184  
Figure 5567: PRO83078  
Figure 5568: DNA273066, NM\_001190,  
gen.NM\_001190  
Figure 5569: PRO61129  
Figure 5570: DNA326740, XM\_058987,  
gen.XM\_058987  
Figure 5571: DNA326741, NM\_000979,  
gen.NM\_000979  
Figure 5572: PRO83080  
Figure 5573: DNA326742, XM\_085935,  
gen.XM\_085935  
Figure 5574: DNA326743, NM\_031485,  
gen.NM\_031485  
Figure 5575: PRO61308  
Figure 5576: DNA103239, NM\_006801,  
gen.NM\_006801  
Figure 5577: PRO4569  
Figure 5578: DNA326744, XM\_046419,  
gen.XM\_046419  
Figure 5579: PRO83082  
Figure 5580: DNA326745, NM\_002691,  
gen.NM\_002691  
Figure 5581: PRO83083  
Figure 5582: DNA326746, XM\_056286,  
gen.XM\_056286  
Figure 5583: PRO83084  
Figure 5584: DNA326747, XM\_058990,  
gen.XM\_058990  
Figure 5585: PRO83085  
Figure 5586: DNA326748, XM\_091981,  
gen.XM\_091981  
Figure 5587: PRO83086  
Figure 5588: DNA326749, NM\_032712,  
gen.NM\_032712  
Figure 5589: PRO23238  
Figure 5590: DNA83154, NM\_001648,  
gen.NM\_001648  
Figure 5591: PRO2109  
Figure 5592: DNA326750, XM\_055658,  
gen.XM\_055658



Figure 5593: DNA269481, NM\_001985,  
gen.NM\_001985  
Figure 5594: PRO57901  
Figure 5595: DNA326751, XM\_091886,  
gen.XM\_091886  
Figure 5596: PRO83087  
Figure 5597: DNA326752, XM\_008830,  
gen.XM\_008830  
Figure 5598: DNA326753, XM\_039908,  
gen.XM\_039908  
Figure 5599: PRO83089  
Figure 5600: DNA326754, NM\_015629,  
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Figure 5601: PRO83090  
Figure 5602: DNA326755, XM\_050236,  
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Figure 5603: DNA326756, XM\_050589,  
gen.XM\_050589  
Figure 5604: PRO83092  
Figure 5605: DNA326757, XM\_117128,  
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Figure 5606: PRO83093  
Figure 5607: DNA326758, XM\_059321,  
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Figure 5608: DNA326759, NM\_003283,  
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Figure 5609: PRO83095  
Figure 5610A-B: DNA326760, NM\_014931,  
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Figure 5611: PRO83096  
Figure 5612: DNA326761, XM\_035919,  
gen.XM\_035919  
Figure 5613: DNA326762, NM\_000991,  
gen.NM\_000991  
Figure 5614: PRO83098  
Figure 5615: DNA273346, NM\_014501,  
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Figure 5616: PRO61349  
Figure 5617: DNA326763, NM\_013333,  
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Figure 5618: PRO83099  
Figure 5619: DNA326764, NM\_007279,  
gen.NM\_007279  
Figure 5620: PRO83100  
Figure 5621: DNA326765, NM\_016202,  
gen.NM\_016202  
Figure 5622: PRO83101  
Figure 5623: DNA326766, XM\_034377,  
gen.XM\_034377  
Figure 5624: PRO83102  
Figure 5625: DNA272062, NM\_014453,  
gen.NM\_014453  
Figure 5626: PRO60333  
Figure 5627: DNA254548, NM\_005762,  
gen.NM\_005762  
Figure 5628: PRO49653

Figure 5629: DNA326767, XM\_085972,  
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Figure 5630: PRO83103  
Figure 5631: DNA326768, NM\_032792,  
gen.NM\_032792  
Figure 5632: PRO83104  
Figure 5633: DNA326769, NM\_001009,  
gen.NM\_001009  
Figure 5634: PRO83105  
Figure 5635: DNA326770, XM\_058125,  
gen.XM\_058125  
Figure 5636: DNA326771, NM\_024691,  
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Figure 5637: PRO83107  
Figure 5638: DNA297288, NM\_021158,  
gen.NM\_021158  
Figure 5639: PRO70810  
Figure 5640: DNA304662, NM\_031229,  
gen.NM\_031229  
Figure 5641: PRO71089  
Figure 5642: DNA326772, NM\_031228,  
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Figure 5643: PRO83108  
Figure 5644: DNA326773, XM\_097749,  
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Figure 5645: PRO83109  
Figure 5646: DNA326774, XM\_055993,  
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Figure 5647: DNA326775, XM\_009622,  
gen.XM\_009622  
Figure 5648: DNA326776, NM\_000801,  
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Figure 5649: PRO59142  
Figure 5650: DNA326777, NM\_054014,  
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Figure 5651: PRO59142  
Figure 5652: DNA326778, NM\_016143,  
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Figure 5653: PRO83112  
Figure 5654: DNA287270, NM\_003091,  
gen.NM\_003091  
Figure 5655: PRO69541  
Figure 5656: DNA326779, NM\_052881,  
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Figure 5657: PRO83113  
Figure 5658: DNA326780, XM\_044914,  
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Figure 5659: PRO83114  
Figure 5660: DNA326781, XM\_044915,  
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Figure 5661: DNA326782, NM\_006899,  
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Figure 5662: PRO83116  
Figure 5663: DNA326783, NM\_019609,  
gen.NM\_019609  
Figure 5664: PRO83117

Figure 5665: DNA326784, NM\_021826,  
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Figure 5666: PRO83118  
Figure 5667: DNA326785, XM\_045418,  
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Figure 5668: DNA287261, NM\_017874,  
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Figure 5669: PRO69533  
Figure 5670: DNA326786, XM\_086710,  
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Figure 5671: DNA326787, XM\_045451,  
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Figure 5672: PRO83121  
Figure 5673: DNA326788, XM\_114174,  
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Figure 5674: DNA326789, XM\_045460,  
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Figure 5675: DNA326790, XM\_059268,  
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Figure 5676A-B: DNA271010, NM\_014737,  
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Figure 5677: PRO59339  
Figure 5678: DNA326791, XM\_056035,  
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Figure 5679: DNA83170, NM\_001819,  
gen.NM\_001819  
Figure 5680: PRO2615  
Figure 5681: DNA227348, NM\_019095,  
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Figure 5682: PRO37811  
Figure 5683: DNA326792, NM\_003092,  
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Figure 5684: PRO83125  
Figure 5685: DNA287290, NM\_014426,  
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Figure 5686: PRO69560  
Figure 5687: DNA326793, XM\_086701,  
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Figure 5688: DNA326794, XM\_117209,  
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Figure 5689A-B: DNA326795, XM\_046520,  
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Figure 5690: PRO83128  
Figure 5691: DNA326796, XM\_115846,  
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Figure 5692: PRO83129  
Figure 5693: DNA326797, NM\_080820,  
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Figure 5694: PRO83130  
Figure 5695: DNA326798, XM\_086715,  
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Figure 5696: DNA326799, XM\_092760,  
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Figure 5697: PRO83132  
Figure 5698: DNA326800, NM\_012255,  
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Figure 5699: PRO83133  
Figure 5700: DNA326801, XM\_012970,  
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Figure 5701: DNA326802, XM\_042765,  
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Figure 5702: PRO83135  
Figure 5703: DNA150548, NM\_001247,  
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Figure 5704: PRO12324  
Figure 5705A-B: DNA326803, XM\_009436,  
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Figure 5706: DNA326804, XM\_114178,  
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Figure 5707: PRO83137  
Figure 5708: DNA326805, XM\_046160,  
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Figure 5709: PRO83138  
Figure 5710: DNA326806, XM\_046179,  
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Figure 5711: PRO83139  
Figure 5712: DNA326807, XM\_086745,  
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Figure 5713: DNA326808, NM\_138578,  
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Figure 5714: PRO83141  
Figure 5715: DNA326809, NM\_012112,  
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Figure 5716: PRO83142  
Figure 5717: DNA326810, XM\_086736,  
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Figure 5718: PRO83143  
Figure 5719: DNA326811, NM\_030815,  
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Figure 5720: PRO83144  
Figure 5721A-B: DNA150767, NM\_014742,  
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Figure 5722: PRO12460  
Figure 5723A-B: DNA326812, XM\_047007,  
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Figure 5724: PRO83145  
Figure 5725A-B: DNA326813, XM\_047011,  
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Figure 5726: PRO83146  
Figure 5727A-B: DNA326814, XM\_047018,  
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Figure 5728: DNA326815, XM\_009450,  
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Figure 5729: DNA326816, NM\_033197,  
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Figure 5730: PRO83149  
Figure 5731: DNA326817, XM\_097772,  
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Figure 5732: PRO83150  
Figure 5733: DNA326818, NM\_016732,  
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Figure 5734: DNA97298, NM\_003908,

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Figure 5735: PRO3645  
Figure 5736: DNA326819, NM\_000687,  
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Figure 5737: PRO83152  
Figure 5738: DNA273517, NM\_000178,  
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Figure 5739: PRO61498  
Figure 5740: DNA326820, NM\_018217,  
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Figure 5741: PRO83153  
Figure 5742: DNA326821, NM\_002212,  
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Figure 5743: PRO60945  
Figure 5744A-C: DNA326822, NM\_007186,  
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Figure 5745: DNA226758, NM\_015966,  
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Figure 5746: PRO37221  
Figure 5747: DNA194701, NM\_003915,  
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Figure 5748: PRO24002  
Figure 5749: DNA326823, XM\_113380,  
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Figure 5750: DNA326824, NM\_016558,  
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Figure 5751: PRO83155  
Figure 5752: DNA326825, NM\_015511,  
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Figure 5753: PRO83156  
Figure 5754: DNA326826, XM\_009501,  
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Figure 5755: PRO83157  
Figure 5756: DNA326827, XM\_057236,  
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Figure 5757: DNA326828, NM\_024918,  
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Figure 5758: PRO83159  
Figure 5759: DNA326829, XM\_009642,  
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Figure 5760: DNA194807, NM\_006698,  
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Figure 5761: PRO24077  
Figure 5762: DNA326830, XM\_009686,  
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Figure 5763: DNA326831, NM\_030877,  
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Figure 5764: PRO83161  
Figure 5765: DNA326832, XM\_028806,  
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Figure 5766A-B: DNA326833, XM\_028810,  
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Figure 5767: PRO83163  
Figure 5768: DNA326834, XM\_012931,  
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Figure 5769: DNA326835, NM\_024855,

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Figure 5770: PRO83165  
Figure 5771A-B: DNA227472, NM\_002660,  
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Figure 5772: PRO37935  
Figure 5773: DNA326836, XM\_097727,  
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Figure 5774: DNA103525, NM\_002466,  
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Figure 5775: PRO4852  
Figure 5776: DNA326837, XM\_029810,  
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Figure 5777: PRO83167  
Figure 5778: DNA326838, XM\_029822,  
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Figure 5779: DNA326839, NM\_002638,  
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Figure 5780: PRO2065  
Figure 5781: DNA326840, NM\_003064,  
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Figure 5782: PRO1720  
Figure 5783: DNA326841, NM\_015937,  
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Figure 5784: PRO83169  
Figure 5785: DNA273320, NM\_007019,  
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Figure 5786: PRO61327  
Figure 5787: DNA326842, NM\_033421,  
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Figure 5788: PRO83170  
Figure 5789: DNA88569, NM\_006227,  
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Figure 5790: PRO2420  
Figure 5791: DNA88239, NM\_004994,  
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Figure 5792: PRO2711  
Figure 5793: DNA326843, XM\_057374,  
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Figure 5794: DNA326844, XM\_114163,  
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Figure 5795A-B: DNA326845, XM\_097731,  
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Figure 5796A-B: DNA326846, XM\_030044,  
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Figure 5797: PRO83174  
Figure 5798: DNA326847, NM\_017895,  
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Figure 5799: PRO83175  
Figure 5800: DNA326848, XM\_097713,  
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Figure 5801: PRO83176  
Figure 5802: DNA326849, NM\_005985,  
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Figure 5803: PRO83177  
Figure 5804: DNA326850, NM\_003349,  
gen.NM\_003349

Figure 5805: PRO83178  
Figure 5806: DNA326851, NM\_022442,  
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Figure 5807: PRO83179  
Figure 5808: DNA326852, NM\_005194,  
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Figure 5809: DNA326853, NM\_002827,  
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Figure 5810: PRO38066  
Figure 5811: DNA326854, NM\_003859,  
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Figure 5812: PRO83180  
Figure 5813: DNA326855, XM\_114165,  
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Figure 5814: DNA269526, NM\_001324,  
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Figure 5815: PRO57942  
Figure 5816: DNA326856, XM\_009549,  
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Figure 5817: PRO83182  
Figure 5818: DNA326857, XM\_030621,  
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Figure 5819: DNA326858, XM\_086648,  
gen.XM\_086648  
Figure 5820: PRO83183  
Figure 5821: DNA326859, XM\_009672,  
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Figure 5822: PRO83184  
Figure 5823A-B: DNA326860, XM\_009671,  
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Figure 5824: DNA326861, NM\_004738,  
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Figure 5825: PRO983  
Figure 5826: DNA326862, NM\_016592,  
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Figure 5827: PRO83185  
Figure 5828: DNA326863, NM\_080425,  
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Figure 5829: PRO83186  
Figure 5830: DNA304670, NM\_000516,  
gen.NM\_000516  
Figure 5831: PRO71097  
Figure 5832: DNA326864, NM\_080426,  
gen.NM\_080426  
Figure 5833: PRO83187  
Figure 5834: DNA326865, XM\_030699,  
gen.XM\_030699  
Figure 5835: PRO83188  
Figure 5836: DNA188229, NM\_000114,  
gen.NM\_000114  
Figure 5837: PRO21728  
Figure 5838: DNA326866, NM\_002792,  
gen.NM\_002792  
Figure 5839: PRO83189  
Figure 5840A-B: DNA326867, XM\_037202,  
gen.XM\_037202

Figure 5841: PRO83190  
Figure 5842: DNA326868, XM\_037206,  
gen.XM\_037206  
Figure 5843: PRO83191  
Figure 5844: DNA103486, NM\_007002,  
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Figure 5845: PRO4813  
Figure 5846A-D: DNA326869, XM\_037217,  
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Figure 5847: DNA326870, NM\_001024,  
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Figure 5848: PRO83193  
Figure 5849: DNA326871, NM\_018270,  
gen.NM\_018270  
Figure 5850: PRO83194  
Figure 5851: DNA326872, XM\_028783,  
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Figure 5852: PRO83195  
Figure 5853: DNA326873, NM\_001853,  
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Figure 5854: PRO83196  
Figure 5855: DNA326874, NM\_080796,  
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Figure 5856: PRO83197  
Figure 5857: DNA326875, NM\_022105,  
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Figure 5858: PRO83198  
Figure 5859: DNA326876, NM\_080797,  
gen.NM\_080797  
Figure 5860: PRO83199  
Figure 5861: DNA326877, NM\_018209,  
gen.NM\_018209  
Figure 5862: PRO83200  
Figure 5863A-C: DNA326878, XM\_028834,  
gen.XM\_028834  
Figure 5864: PRO83201  
Figure 5865: DNA326879, NM\_024299,  
gen.NM\_024299  
Figure 5866: PRO83202  
Figure 5867A-C: DNA326880, XM\_028918,  
gen.XM\_028918  
Figure 5868: PRO83203  
Figure 5869: DNA326881, NM\_032527,  
gen.NM\_032527  
Figure 5870: PRO83204  
Figure 5871A-B: DNA326882, XM\_028966,  
gen.XM\_028966  
Figure 5872: PRO83205  
Figure 5873: DNA269746, NM\_012469,  
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Figure 5874: PRO58155  
Figure 5875: DNA326883, XM\_114154,  
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Figure 5876: DNA326884, XM\_072173,  
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Figure 5877: DNA326885, XM\_086759,

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 Figure 5878: DNA326886, XM\_086760,  
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 Figure 5879: DNA326887, NM\_021219,  
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 Figure 5880: PRO28687  
 Figure 5881: DNA188732, NM\_000484,  
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 Figure 5882: PRO25302  
 Figure 5883: DNA326888, NM\_016940,  
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 Figure 5884: PRO83210  
 Figure 5885: DNA254572, NM\_006585,  
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 Figure 5886: PRO49675  
 Figure 5887: DNA326889, NM\_005806,  
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 Figure 5888: PRO83211  
 Figure 5889: DNA326890, XM\_114185,  
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 Figure 5890: DNA254994, NM\_017613,  
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 Figure 5891: PRO50083  
 Figure 5892: DNA274129, NM\_001697,  
 gen.NM\_001697  
 Figure 5893: PRO62065  
 Figure 5894: DNA326891, NM\_001757,  
 gen.NM\_001757  
 Figure 5895: PRO83212  
 Figure 5896A-C: DNA151898, NM\_003316,  
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 Figure 5897: PRO12135  
 Figure 5898: DNA326892, NM\_003720,  
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 Figure 5899: PRO83213  
 Figure 5900: DNA326893, NM\_002606,  
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 Figure 5901: PRO83214  
 Figure 5902: DNA326894, XM\_033015,  
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 Figure 5903: DNA326895, XM\_033016,  
 gen.XM\_033016  
 Figure 5904: PRO59669  
 Figure 5905: DNA326896, NM\_003681,  
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 Figure 5906: PRO69486  
 Figure 5907: DNA326897, XM\_035999,  
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 Figure 5908: DNA326898, NM\_020132,  
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 Figure 5909: PRO83217  
 Figure 5910: DNA326899, XM\_036011,  
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 Figure 5911: DNA326900, NM\_013369,  
 gen.NM\_013369  
 Figure 5912: PRO83219

Figure 5913: DNA326901, XM\_036042,  
 gen.XM\_036042  
 Figure 5914: DNA326902, XM\_086770,  
 gen.XM\_086770  
 Figure 5915: DNA326903, NM\_004928,  
 gen.NM\_004928  
 Figure 5916: PRO83222  
 Figure 5917: DNA326904, XM\_036087,  
 gen.XM\_036087  
 Figure 5918: PRO83223  
 Figure 5919: DNA326905, XM\_009805,  
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 Figure 5920: PRO83224  
 Figure 5921: DNA226409, NM\_004339,  
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 Figure 5922: PRO36872  
 Figure 5923: DNA326906, XM\_036107,  
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 Figure 5924A-B: DNA326907, XM\_036175,  
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 Figure 5925: DNA326908, XM\_097817,  
 gen.XM\_097817  
 Figure 5926A-B: DNA326909, XM\_054566,  
 gen.XM\_054566  
 Figure 5927: DNA326910, XM\_036755,  
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 Figure 5928: DNA326911, XM\_086773,  
 gen.XM\_086773  
 Figure 5929: DNA326912, XM\_097807,  
 gen.XM\_097807  
 Figure 5930: DNA326913, XM\_086777,  
 gen.XM\_086777  
 Figure 5931: DNA326914, NM\_002340,  
 gen.NM\_002340  
 Figure 5932: PRO83233  
 Figure 5933A-B: DNA326915, NM\_003906,  
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 Figure 5934: PRO83234  
 Figure 5935: DNA226617, NM\_006272,  
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 Figure 5936: PRO37080  
 Figure 5937: DNA326916, NM\_033070,  
 gen.NM\_033070  
 Figure 5938: PRO83235  
 Figure 5939: DNA255046, NM\_017829,  
 gen.NM\_017829  
 Figure 5940: PRO50134  
 Figure 5941: DNA326917, NM\_001696,  
 gen.NM\_001696  
 Figure 5942: PRO83236  
 Figure 5943A-B: DNA326918, XM\_032996,  
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 Figure 5944: PRO83237  
 Figure 5945: DNA326919, XM\_167538,  
 gen.XM\_167538  
 Figure 5946: DNA326920, XM\_033090,

gen.XM\_033090  
 Figure 5947: DNA225954, NM\_000407,  
 gen.NM\_000407  
 Figure 5948: PRO36417  
 Figure 5949: DNA326921, XM\_058918,  
 gen.XM\_058918  
 Figure 5950: DNA326922, XM\_097833,  
 gen.XM\_097833  
 Figure 5951: DNA326923, NM\_024627,  
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 Figure 5952: PRO83242  
 Figure 5953: DNA326924, XM\_086809,  
 gen.XM\_086809  
 Figure 5954: DNA326925, NM\_006440,  
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 Figure 5955: PRO83244  
 Figure 5956: DNA226561, NM\_000754,  
 gen.NM\_000754  
 Figure 5957: PRO37024  
 Figure 5958: DNA326926, NM\_007310,  
 gen.NM\_007310  
 Figure 5959: PRO83245  
 Figure 5960A-B: DNA326927, XM\_033813,  
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 Figure 5961: DNA326928, NM\_022727,  
 gen.NM\_022727  
 Figure 5962: PRO83247  
 Figure 5963: DNA326929, XM\_086805,  
 gen.XM\_086805  
 Figure 5964: DNA326930, XM\_086873,  
 gen.XM\_086873  
 Figure 5965: DNA257549, NM\_030573,  
 gen.NM\_030573  
 Figure 5966: PRO52119  
 Figure 5967: DNA326931, XM\_096155,  
 gen.XM\_096155  
 Figure 5968: DNA326932, XM\_096156,  
 gen.XM\_096156  
 Figure 5969A-B: DNA326933, XM\_036937,  
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 Figure 5970: PRO83252  
 Figure 5971: DNA326934, XM\_097886,  
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 Figure 5972: PRO83253  
 Figure 5973: DNA304835, NM\_022044,  
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 Figure 5974: PRO71242  
 Figure 5975: DNA326935, NM\_006115,  
 gen.NM\_006115  
 Figure 5976: PRO37012  
 Figure 5977: DNA326936, XM\_037682,  
 gen.XM\_037682  
 Figure 5978: PRO83254  
 Figure 5979: DNA326937, NM\_002415,  
 gen.NM\_002415  
 Figure 5980: PRO83255

Figure 5981A-B: DNA326938, XM\_037797,  
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 Figure 5982: PRO83256  
 Figure 5983: DNA326939, NM\_004175,  
 gen.NM\_004175  
 Figure 5984: PRO83257  
 Figure 5985: DNA326940, XM\_086821,  
 gen.XM\_086821  
 Figure 5986: DNA326941, XM\_092888,  
 gen.XM\_092888  
 Figure 5987: DNA326942, NM\_005080,  
 gen.NM\_005080  
 Figure 5988: PRO83260  
 Figure 5989: DNA269830, NM\_005243,  
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 Figure 5990: PRO58232  
 Figure 5991: DNA326943, NM\_006478,  
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 Figure 5992: PRO83261  
 Figure 5993A-B: DNA326944, XM\_037945,  
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 Figure 5994: DNA103462, NM\_000268,  
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 Figure 5995: PRO4789  
 Figure 5996: DNA326945, NM\_032204,  
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 Figure 5997: PRO83263  
 Figure 5998: DNA326946, XM\_066291,  
 gen.XM\_066291  
 Figure 5999: DNA326947, NM\_005877,  
 gen.NM\_005877  
 Figure 6000: PRO62328  
 Figure 6001: DNA326948, NM\_016498,  
 gen.NM\_016498  
 Figure 6002: PRO83265  
 Figure 6003: DNA254141, NM\_014303,  
 gen.NM\_014303  
 Figure 6004: PRO49256  
 Figure 6005A-B: DNA151882, NM\_014941,  
 gen.NM\_014941  
 Figure 6006: PRO12134  
 Figure 6007: DNA326949, NM\_006932,  
 gen.NM\_006932  
 Figure 6008: PRO83266  
 Figure 6009: DNA326950, NM\_134269,  
 gen.NM\_134269  
 Figure 6010: PRO83267  
 Figure 6011: DNA270697, NM\_004147,  
 gen.NM\_004147  
 Figure 6012: PRO59061  
 Figure 6013: DNA326951, XM\_059335,  
 gen.XM\_059335  
 Figure 6014: DNA326952, XM\_018539,  
 gen.XM\_018539  
 Figure 6015: DNA326953, NM\_014306,  
 gen.NM\_014306

Figure 6016: PRO83270  
Figure 6017: DNA326954, NM\_012179,  
gen.NM\_012179  
Figure 6018: PRO83271  
Figure 6019A-B: DNA326955, XM\_038584,  
gen.XM\_038584  
Figure 6020: DNA151752, NM\_002133,  
gen.NM\_002133  
Figure 6021: PRO12886  
Figure 6022: DNA326956, XM\_009947,  
gen.XM\_009947  
Figure 6023: PRO12845  
Figure 6024: DNA326957, XM\_114209,  
gen.XM\_114209  
Figure 6025A-B: DNA326958, NM\_002473,  
gen.NM\_002473  
Figure 6026: PRO83273  
Figure 6027: DNA188740, NM\_003753,  
gen.NM\_003753  
Figure 6028: PRO22481  
Figure 6029: DNA326959, NM\_021126,  
gen.NM\_021126  
Figure 6030: PRO70331  
Figure 6031: DNA326960, XM\_009967,  
gen.XM\_009967  
Figure 6032: DNA326961, NM\_013365,  
gen.NM\_013365  
Figure 6033: PRO83274  
Figure 6034: DNA290259, NM\_018957,  
gen.NM\_018957  
Figure 6035: PRO70383  
Figure 6036: DNA326962, NM\_020315,  
gen.NM\_020315  
Figure 6037: PRO83275  
Figure 6038: DNA304719, NM\_002305,  
gen.NM\_002305  
Figure 6039: PRO71145  
Figure 6040: DNA326963, NM\_007032,  
gen.NM\_007032  
Figure 6041: PRO83276  
Figure 6042: DNA326964, XM\_009973,  
gen.XM\_009973  
Figure 6043: DNA326965, XM\_086830,  
gen.XM\_086830  
Figure 6044: PRO83278  
Figure 6045: DNA254240, NM\_016091,  
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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTSI. Definitions

The terms "TAT polypeptide" and "TAT" as used herein and when immediately followed by a numerical designation, refer to various polypeptides, wherein the complete designation (i.e., TAT/number) refers to specific polypeptide sequences as described herein. The terms "TAT/number polypeptide" and "TAT/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides, polypeptide variants and fragments of native sequence polypeptides and polypeptide variants (which are further defined herein). The TAT polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "TAT polypeptide" refers to each individual TAT/number polypeptide disclosed herein. All disclosures in this specification which refer to the "TAT polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, formation of TAT binding oligopeptides to or against, formation of TAT binding organic molecules to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "TAT polypeptide" also includes variants of the TAT/number polypeptides disclosed herein.

A "native sequence TAT polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding TAT polypeptide derived from nature. Such native sequence TAT polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence TAT polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific TAT polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In certain embodiments of the invention, the native sequence TAT polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons (if indicated) are shown in bold font and underlined in the figures. Nucleic acid residues indicated as "N" in the accompanying figures are any nucleic acid residue. However, while the TAT polypeptides disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the TAT polypeptides.

The TAT polypeptide "extracellular domain" or "ECD" refers to a form of the TAT polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a TAT polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the TAT polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an

extracellular domain of a TAT polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various TAT polypeptides disclosed herein may be shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"TAT polypeptide variant" means a TAT polypeptide, preferably an active TAT polypeptide, as defined herein having at least about 80% amino acid sequence identity with a full-length native sequence TAT polypeptide sequence as disclosed herein, a TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length TAT polypeptide). Such TAT polypeptide variants include, for instance, TAT polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a TAT polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to a full-length native sequence TAT polypeptide sequence as disclosed herein, a TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide sequence as disclosed herein. Ordinarily, TAT variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 amino acids in length, or more. Optionally, TAT variant polypeptides will have no more than one conservative amino acid substitution as compared to the native TAT polypeptide sequence, alternatively no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to the native TAT polypeptide sequence.

"Percent (%) amino acid sequence identity" with respect to the TAT polypeptide sequences identified

herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific TAT polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "TAT", wherein "TAT" represents the amino acid sequence of a hypothetical TAT polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "TAT" polypeptide of interest is being compared, and "X," "Y" and "Z" each represent different hypothetical amino acid residues. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

"TAT variant polynucleotide" or "TAT variant nucleic acid sequence" means a nucleic acid molecule

which encodes a TAT polypeptide, preferably an active TAT polypeptide, as defined herein and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence TAT polypeptide sequence as disclosed herein, a full-length native sequence TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length TAT polypeptide). Ordinarily, a TAT variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence TAT polypeptide sequence as disclosed herein, a full-length native sequence TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, TAT variant polynucleotides are at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

"Percent (%) nucleic acid sequence identity" with respect to TAT-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the TAT nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison

parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

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$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "TAT-DNA", wherein "TAT-DNA" represents a hypothetical TAT-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "TAT-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides. Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

In other embodiments, TAT variant polynucleotides are nucleic acid molecules that encode a TAT polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length TAT polypeptide as disclosed herein. TAT variant polypeptides may be those that are encoded by a TAT variant polynucleotide.

The term "full-length coding region" when used in reference to a nucleic acid encoding a TAT polypeptide refers to the sequence of nucleotides which encode the full-length TAT polypeptide of the invention (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures). The term "full-length coding region" when used in reference to an ATCC deposited nucleic acid refers to the TAT polypeptide-encoding portion of the cDNA that is inserted into the vector deposited with the ATCC (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures).

"Isolated," when used to describe the various TAT polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or,



preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the TAT polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" TAT polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium

chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) overnight hybridization in a solution that employs 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with a 10 minute wash at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) followed by a 10 minute high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a TAT polypeptide or anti-TAT antibody fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

"Active" or "activity" for the purposes herein refers to form(s) of a TAT polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring TAT, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring TAT other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring TAT and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring TAT.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native TAT polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native TAT polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native TAT polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a TAT polypeptide may comprise contacting a TAT polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities

normally associated with the TAT polypeptide.

"Treating" or "treatment" or "alleviation" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. A subject or mammal is successfully "treated" for a TAT polypeptide-expressing cancer if, after receiving a therapeutic amount of an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule according to the methods of the present invention, the patient shows observable and/or measurable reduction in or absence of one or more of the following: reduction in the number of cancer cells or absence of the cancer cells; reduction in the tumor size; inhibition (i.e., slow to some extent and preferably stop) of cancer cell infiltration into peripheral organs including the spread of cancer into soft tissue and bone; inhibition (i.e., slow to some extent and preferably stop) of tumor metastasis; inhibition, to some extent, of tumor growth; and/or relief to some extent, one or more of the symptoms associated with the specific cancer; reduced morbidity and mortality, and improvement in quality of life issues. To the extent the anti-TAT antibody or TAT binding oligopeptide may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. Reduction of these signs or symptoms may also be felt by the patient.

The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR). Metastasis can be determined by staging tests and by bone scan and tests for calcium level and other enzymes to determine spread to the bone. CT scans can also be done to look for spread to the pelvis and lymph nodes in the area. Chest X-rays and measurement of liver enzyme levels by known methods are used to look for metastasis to the lungs and liver, respectively. Other routine methods for monitoring the disease include transrectal ultrasonography (TRUS) and transrectal needle biopsy (TRNB).

For bladder cancer, which is a more localized cancer, methods to determine progress of disease include urinary cytologic evaluation by cystoscopy, monitoring for presence of blood in the urine, visualization of the urothelial tract by sonography or an intravenous pyelogram, computed tomography (CT) and magnetic resonance imaging (MRI). The presence of distant metastases can be assessed by CT of the abdomen, chest x-rays, or radionuclide imaging of the skeleton.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of the treatment of, alleviating the symptoms of or diagnosis of a cancer refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous

(concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®.

By "solid phase" or "solid support" is meant a non-aqueous matrix to which an antibody, TAT binding oligopeptide or TAT binding organic molecule of the present invention can adhere or attach. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a TAT polypeptide, an antibody thereto or a TAT binding oligopeptide) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small" molecule or "small" organic molecule is defined herein to have a molecular weight below about 500 Daltons.

An "effective amount" of a polypeptide, antibody, TAT binding oligopeptide, TAT binding organic molecule or an agonist or antagonist thereof as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" may be determined empirically and in a routine manner, in relation to the stated purpose.

The term "therapeutically effective amount" refers to an amount of an antibody, polypeptide, TAT binding oligopeptide, TAT binding organic molecule or other drug effective to "treat" a disease or disorder in a subject or mammal. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. See the definition herein of "treating". To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic.

A "growth inhibitory amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide

or TAT binding organic molecule is an amount capable of inhibiting the growth of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "growth inhibitory amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule for purposes of inhibiting neoplastic cell growth may be determined empirically and in a routine manner.

5 A "cytotoxic amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule is an amount capable of causing the destruction of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "cytotoxic amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule for purposes of inhibiting neoplastic cell growth may be determined empirically and in a routine manner.

10 The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-TAT monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-TAT antibody compositions with polyepitopic specificity, polyclonal antibodies, single chain anti-TAT antibodies, and fragments of anti-TAT antibodies (see below) as long as they exhibit the desired biological or immunological activity. The term "immunoglobulin" (Ig) is used interchangeable with antibody herein.

15 An "isolated antibody" is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

25 The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to a H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain ( $V_H$ ) followed by three constant domains ( $C_H$ ) for each of the  $\alpha$  and  $\gamma$  chains and four  $C_H$  domains for  $\mu$  and  $\epsilon$  isotypes. Each L chain has at the N-terminus, a variable domain ( $V_L$ ) followed by a constant domain ( $C_L$ ) at its other end. The  $V_L$  is aligned with the  $V_H$  and the  $C_L$  is aligned with the first constant domain of the heavy chain ( $C_{H1}$ ). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a  $V_H$  and  $V_L$  together forms a single antigen-binding site. For the structure and properties of the

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different classes of antibodies, see, e.g., Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains ( $C_H$ ), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated  $\alpha$ ,  $\delta$ ,  $\epsilon$ ,  $\gamma$ , and  $\mu$ , respectively. The  $\gamma$  and  $\alpha$  classes are further divided into subclasses on the basis of relatively minor differences in  $C_H$  sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

The term "variable" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and define specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a  $\beta$ -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the  $\beta$ -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the  $V_L$ , and around about 1-35 (H1), 50-65 (H2) and 95-102 (H3) in the  $V_H$ ; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, (1991)) and/or those residues from a "hypervariable loop" (e.g. residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the  $V_L$ , and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the  $V_H$ ; Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)).

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies.

The modifier "monoclonal" is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology first described by Kohler et al., Nature, 256:495 (1975), or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, e.g., U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991), for example.

The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Patent No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey, Ape etc), and human constant region sequences.

An "intact" antibody is one which comprises an antigen-binding site as well as a C<sub>L</sub> and at least heavy chain constant domains, C<sub>H</sub>1, C<sub>H</sub>2 and C<sub>H</sub>3. The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')<sub>2</sub>, and Fv fragments; diabodies; linear antibodies (see U.S. Patent No. 5,641,870, Example 2; Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V<sub>H</sub>), and the first constant domain of one heavy chain (C<sub>H</sub>1). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large F(ab')<sub>2</sub> fragment which roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C<sub>H</sub>1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')<sub>2</sub> antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides.

The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the V<sub>H</sub> and V<sub>L</sub> antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V<sub>H</sub> and V<sub>L</sub> domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, *infra*.

The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the V<sub>H</sub> and V<sub>L</sub> domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V<sub>H</sub> and V<sub>L</sub> domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993).

"Humanized" forms of non-human (e.g., rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

A "species-dependent antibody," e.g., a mammalian anti-human IgE antibody, is an antibody which



has a stronger binding affinity for an antigen from a first mammalian species than it has for a homologue of that antigen from a second mammalian species. Normally, the species-dependent antibody "bind specifically" to a human antigen (i.e., has a binding affinity (Kd) value of no more than about  $1 \times 10^{-7}$  M, preferably no more than about  $1 \times 10^{-8}$  and most preferably no more than about  $1 \times 10^{-9}$  M) but has a binding affinity for a homologue of the antigen from a second non-human mammalian species which is at least about 50 fold, or at least about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The species-dependent antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody.

A "TAT binding oligopeptide" is an oligopeptide that binds, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be chemically synthesized using known oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. TAT binding oligopeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such oligopeptides that are capable of binding, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in the art (see, e.g., U.S. Patent Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 81:3998-4002 (1984); Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 82:178-182 (1985); Geysen et al., in *Synthetic Peptides as Antigens*, 130-149 (1986); Geysen et al., J. Immunol. Meth., 102:259-274 (1987); Schoofs et al., J. Immunol., 140:611-616 (1988), Cwirla, S. E. et al. (1990) Proc. Natl. Acad. Sci. USA, 87:6378; Lowman, H.B. et al. (1991) Biochemistry, 30:10832; Clackson, T. et al. (1991) Nature, 352: 624; Marks, J. D. et al. (1991), J. Mol. Biol., 222:581; Kang, A.S. et al. (1991) Proc. Natl. Acad. Sci. USA, 88:8363, and Smith, G. P. (1991) Current Opin. Biotechnol., 2:668).

A "TAT binding organic molecule" is an organic molecule other than an oligopeptide or antibody as defined herein that binds, preferably specifically, to a TAT polypeptide as described herein. TAT binding organic molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). TAT binding organic molecules are usually less than about 2000 daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 daltons in size, wherein such organic molecules that are capable of binding, preferably specifically, to a TAT polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585).

An antibody, oligopeptide or other organic molecule "which binds" an antigen of interest, e.g. a tumor-associated polypeptide antigen target, is one that binds the antigen with sufficient affinity such that the antibody, oligopeptide or other organic molecule is useful as a diagnostic and/or therapeutic agent in targeting a cell or tissue expressing the antigen, and does not significantly cross-react with other proteins. In such embodiments, the extent of binding of the antibody, oligopeptide or other organic molecule to a "non-target" protein will be less than about 10% of the binding of the antibody, oligopeptide or other organic molecule to its particular target protein as determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA). With regard to the binding of an antibody, oligopeptide or other organic molecule to a target molecule, the term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a  $K_d$  for the target of at least about  $10^{-4}$  M, alternatively at least about  $10^{-5}$  M, alternatively at least about  $10^{-6}$  M, alternatively at least about  $10^{-7}$  M, alternatively at least about  $10^{-8}$  M, alternatively at least about  $10^{-9}$  M, alternatively at least about  $10^{-10}$  M, alternatively at least about  $10^{-11}$  M, alternatively at least about  $10^{-12}$  M, or greater. In one embodiment, the term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

An antibody, oligopeptide or other organic molecule that "inhibits the growth of tumor cells expressing a TAT polypeptide" or a "growth inhibitory" antibody, oligopeptide or other organic molecule is one which results in measurable growth inhibition of cancer cells expressing or overexpressing the appropriate TAT polypeptide. The TAT polypeptide may be a transmembrane polypeptide expressed on the surface of a cancer cell or may be a polypeptide that is produced and secreted by a cancer cell. Preferred growth inhibitory anti-TAT antibodies, oligopeptides or organic molecules inhibit growth of TAT-expressing tumor cells by greater

than 20%, preferably from about 20% to about 50%, and even more preferably, by greater than 50% (e.g., from about 50% to about 100%) as compared to the appropriate control, the control typically being tumor cells not treated with the antibody, oligopeptide or other organic molecule being tested. In one embodiment, growth inhibition can be measured at an antibody concentration of about 0.1 to 30  $\mu\text{g/ml}$  or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the antibody. Growth inhibition of tumor cells *in vivo* can be determined in various ways such as is described in the Experimental Examples section below. The antibody is growth inhibitory *in vivo* if administration of the anti-TAT antibody at about 1  $\mu\text{g/kg}$  to about 100  $\text{mg/kg}$  body weight results in reduction in tumor size or tumor cell proliferation within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

An antibody, oligopeptide or other organic molecule which "induces apoptosis" is one which induces programmed cell death as determined by binding of annexin V, fragmentation of DNA, cell shrinkage, dilation of endoplasmic reticulum, cell fragmentation, and/or formation of membrane vesicles (called apoptotic bodies). The cell is usually one which overexpresses a TAT polypeptide. Preferably the cell is a tumor cell, e.g., a prostate, breast, ovarian, stomach, endometrial, lung, kidney, colon, bladder cell. Various methods are available for evaluating the cellular events associated with apoptosis. For example, phosphatidyl serine (PS) translocation can be measured by annexin binding; DNA fragmentation can be evaluated through DNA laddering; and nuclear/chromatin condensation along with DNA fragmentation can be evaluated by any increase in hypodiploid cells. Preferably, the antibody, oligopeptide or other organic molecule which induces apoptosis is one which results in about 2 to 50 fold, preferably about 5 to 50 fold, and most preferably about 10 to 50 fold, induction of annexin binding relative to untreated cell in an annexin binding assay.

Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

"Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies "arm" the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express Fc $\gamma$ RIII only, whereas monocytes express Fc $\gamma$ RI, Fc $\gamma$ RII and Fc $\gamma$ RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, Annu. Rev. Immunol. 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in a animal model such as that disclosed in Clynes et al.

(USA) 95:652-656 (1998).

"Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc $\gamma$ RI, Fc $\gamma$ RII and Fc $\gamma$ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc $\gamma$ RII receptors include Fc $\gamma$ RIIA (an "activating receptor") and Fc $\gamma$ RIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc  $\gamma$ RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc $\gamma$ RIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (see review M. in Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)).

"Human effector cells" are leukocytes which express one or more FcRs and perform effector functions. Preferably, the cells express at least Fc  $\gamma$ RIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells may be isolated from a native source, e.g., from blood.

"Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996), may be performed.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, multiple myeloma and B-cell lymphoma, brain, as well as head and neck cancer, and associated metastases.

The terms "cell proliferative disorder" and "proliferative disorder" refer to disorders that are

associated with some degree of abnormal cell proliferation. In one embodiment, the cell proliferative disorder is cancer.

"Tumor", as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

An antibody, oligopeptide or other organic molecule which "induces cell death" is one which causes a viable cell to become nonviable. The cell is one which expresses a TAT polypeptide, preferably a cell that overexpresses a TAT polypeptide as compared to a normal cell of the same tissue type. The TAT polypeptide may be a transmembrane polypeptide expressed on the surface of a cancer cell or may be a polypeptide that is produced and secreted by a cancer cell. Preferably, the cell is a cancer cell, e.g., a breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, thyroid, pancreatic or bladder cell. Cell death *in vitro* may be determined in the absence of complement and immune effector cells to distinguish cell death induced by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Thus, the assay for cell death may be performed using heat inactivated serum (i.e., in the absence of complement) and in the absence of immune effector cells. To determine whether the antibody, oligopeptide or other organic molecule is able to induce cell death, loss of membrane integrity as evaluated by uptake of propidium iodide (PI), trypan blue (see Moore et al. Cytotechnology 17:1-11 (1995)) or 7AAD can be assessed relative to untreated cells. Preferred cell death-inducing antibodies, oligopeptides or other organic molecules are those which induce PI uptake in the PI uptake assay in BT474 cells.

A "TAT-expressing cell" is a cell which expresses an endogenous or transfected TAT polypeptide either on the cell surface or in a secreted form. A "TAT-expressing cancer" is a cancer comprising cells that have a TAT polypeptide present on the cell surface or that produce and secrete a TAT polypeptide. A "TAT-expressing cancer" optionally produces sufficient levels of TAT polypeptide on the surface of cells thereof, such that an anti-TAT antibody, oligopeptide or other organic molecule can bind thereto and have a therapeutic effect with respect to the cancer. In another embodiment, a "TAT-expressing cancer" optionally produces and secretes sufficient levels of TAT polypeptide, such that an anti-TAT antibody, oligopeptide or other organic molecule antagonist can bind thereto and have a therapeutic effect with respect to the cancer. With regard to the latter, the antagonist may be an antisense oligonucleotide which reduces, inhibits or prevents production and secretion of the secreted TAT polypeptide by tumor cells. A cancer which "overexpresses" a TAT polypeptide is one which has significantly higher levels of TAT polypeptide at the cell surface thereof, or produces and secretes, compared to a noncancerous cell of the same tissue type. Such overexpression may be caused by gene amplification or by increased transcription or translation. TAT polypeptide overexpression may be determined in a diagnostic or prognostic assay by evaluating increased levels of the TAT protein present on the surface of a cell, or secreted by the cell (e.g., via an immunohistochemistry assay using anti-TAT antibodies prepared against an isolated TAT polypeptide which may be prepared using recombinant DNA technology from an isolated nucleic acid encoding the TAT polypeptide; FACS analysis, etc.). Alternatively, or additionally, one may measure levels of TAT polypeptide-encoding nucleic acid or mRNA in the cell, e.g., via fluorescent *in situ* hybridization using a nucleic acid based probe corresponding to a TAT-encoding nucleic acid or the complement

thereof; (FISH; see WO98/45479 published October, 1998), Southern blotting, Northern blotting, or polymerase chain reaction (PCR) techniques, such as real time quantitative PCR (RT-PCR). One may also study TAT polypeptide overexpression by measuring shed antigen in a biological fluid such as serum, e.g. using antibody-based assays (see also, e.g., U.S. Patent No. 4,933,294 issued June 12, 1990; WO91/05264 published April 18, 1991; U.S. Patent 5,401,638 issued March 28, 1995; and Sias et al., J. Immunol. Methods 132:73-80 (1990)). Aside from the above assays, various *in vivo* assays are available to the skilled practitioner. For example, one may expose cells within the body of the patient to an antibody which is optionally labeled with a detectable label, e.g., a radioactive isotope, and binding of the antibody to cells in the patient can be evaluated, e.g., by external scanning for radioactivity or by analyzing a biopsy taken from a patient previously exposed to the antibody.

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody, oligopeptide or other organic molecule so as to generate a "labeled" antibody, oligopeptide or other organic molecule. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g.,  $^{211}\text{At}$ ,  $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{90}\text{Y}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{153}\text{Sm}$ ,  $^{212}\text{Bi}$ ,  $^{32}\text{P}$  and radioactive isotopes of Lu), chemotherapeutic agents e.g. methotrexate, adriamycin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents, enzymes and fragments thereof such as nucleolytic enzymes, antibiotics, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof, and the various antitumor or anticancer agents disclosed below. Other cytotoxic agents are described below. A tumoricidal agent causes destruction of tumor cells.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially a TAT-expressing cancer cell, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent may be one which significantly reduces the percentage of TAT-expressing cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such

as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb). Paclitaxel and docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

"Doxorubicin" is an anthracycline antibiotic. The full chemical name of doxorubicin is (8S-cis)-10-[(3-amino-2,3,6-trideoxy- $\alpha$ -L-lyxo-hexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione.

The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prolaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- $\alpha$  and - $\beta$ ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- $\beta$ ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- $\alpha$  and TGF- $\beta$ ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon - $\alpha$ , - $\beta$ , and - $\gamma$ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- $\alpha$  or TNF- $\beta$ ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.



Table 1

```

/*
*
* C-C increased from 12 to 15
* Z is average of EQ
5  * B is average of ND
* match with stop is _M; stop-stop = 0; J (joker) match = 0
*/
#define _M      -8      /* value of a match with a stop */

10 int  _day[26][26] = {
/*  A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */  { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
/* B */  { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
/* C */  {-2, -4, 15, -5, -5, -4, -3, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
15 /* D */  { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
/* E */  { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
/* F */  {-4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
/* G */  { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
/* H */  {-1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
20 /* I */  {-1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
/* J */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */  {-1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
/* L */  {-2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
/* M */  {-1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
25 /* N */  { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
/* O */  {_M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, 0, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */  { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
/* Q */  { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
/* R */  {-2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, -3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
30 /* S */  { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
/* T */  { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
/* U */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */  { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
/* W */  {-6, -5, -8, -7, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
35 /* X */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */  {-3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
/* Z */  { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};
40

45

50

```

**Table 1 (cont')**

```

/*
*/
#include <stdio.h>
#include <ctype.h>

5
#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
10
#define MX          4       /* save if there's at least MX-1 bases since last jmp */

#define DMAT         3      /* value of matching bases */
#define DMIS         0      /* penalty for mismatched bases */
#define DINS0        8      /* penalty for a gap */
15
#define DINS1        1      /* penalty per base */
#define PINS0        8      /* penalty for a gap */
#define PINS1        4      /* penalty per residue */

struct jmp {
20
    short            n[MAXJMP]; /* size of jmp (neg for dely) */
    unsigned short   x[MAXJMP]; /* base no. of jmp in seq x */
}; /* limits seq to 2^16 -1 */

struct diag {
25
    int              score;      /* score at last jmp */
    long             offset;     /* offset of prev block */
    short            ijmp;       /* current jmp index */
    struct jmp        jp;        /* list of jmps */
};

30
struct path {
    int              spc;        /* number of leading spaces */
    short            n[JMPS];    /* size of jmp (gap) */
    int              x[JMPS];    /* loc of jmp (last elem before gap) */
};

35
char              *ofile;       /* output file name */
char              *namex[2];    /* seq names: getseqs() */
char              *prog;        /* prog name for err msgs */
char              *seqx[2];     /* seqs: getseqs() */
40
int               dmax;         /* best diag: nw() */
int               dmax0;        /* final diag */
int               dna;          /* set if dna: main() */
int               endgaps;      /* set if penalizing end gaps */
int               gapx, gapy;    /* total gaps in seqs */
45
int               len0, len1;    /* seq lens */
int               ngapx, ngapy;  /* total size of gaps */
int               smax;         /* max score: nw() */
int               *xbm;         /* bitmap for matching */
long              offset;       /* current offset in jmp file */
50
struct            diag          *dx; /* holds diagonals */
struct            path          pp[2]; /* holds path for seqs */

char              *calloc(), *malloc(), *index(), *strcpy();
char              *getseq(), *g_calloc();

```

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
* where file1 and file2 are two dna or two protein sequences.
* The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
* Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
#include "nw.h"
#include "day.h"

static _dbval[26] = {
    1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
    1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
    1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
    1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
int ac;
char *av[];
{
    prog = av[0];
    if (ac != 3) {
        fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
        fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
    }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
    xbm = (dna)? _dbval : _pbval;

    endgaps = 0; /* 1 to penalize endgaps */
    ofile = "align.out"; /* output file */

    nw(); /* fill in the matrix, get the possible jumps */
    readjumps(); /* get the actual jumps */
    print(); /* print stats, alignment */

    cleanup(0); /* unlink any tmp files */
}

```

**Table 1 (cont')**

```

/* do the alignment, return best score: main()
* dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
* pro: PAM 250 values
* When scores are equal, we prefer mismatches to any gap, prefer
5 * a new gap to extending an ongoing gap, and prefer a gap in seqx
* to a gap in seq y.
*/
nw()
{
10     char      *px, *py;          /* seqs and ptrs */
     int        *ndely, *dely;     /* keep track of dely */
     int        ndelx, delx;       /* keep track of delx */
     int        *tmp;             /* for swapping row0, row1 */
     int        mis;              /* score for each type */
15     int        ins0, ins1;       /* insertion penalties */
     register   id;               /* diagonal index */
     register   ij;              /* jmp index */
     register   *col0, *col1;     /* score for curr, last row */
     register   xx, yy;           /* index into seqs */
20
     dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));
     ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
     dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
     col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
25     col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
     ins0 = (dna)? DINS0 : PINS0;
     ins1 = (dna)? DINS1 : PINS1;
     smax = -10000;
     if (endgaps) {
30         for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
             col0[yy] = dely[yy] = col0[yy-1] - ins1;
             ndely[yy] = yy;
         }
         col0[0] = 0;          /* Waterman Bull Math Biol 84 */
35     }
     else
         for (yy = 1; yy <= len1; yy++)
             dely[yy] = -ins0;

     /* fill in match matrix
     */
40     for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
         /* initialize first entry in col
         */
         if (endgaps) {
45             if (xx == 1)
                 col1[0] = delx = -(ins0+ins1);
             else
                 col1[0] = delx = col0[0] - ins1;
             ndelx = xx;
50         }
         else {
             col1[0] = 0;
             delx = -ins0;
             ndelx = 0;
55         }
     }

```

Table 1 (cont')

...NW

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongong del
     * ignore MAXGAP if weighting endgaps
     */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
     * favor new del over ongong del
     */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
     * mis over any del and delx over dely
     */

    id = xx - yy + len1 - 1;
    if (mis >= delx && mis >= dely[yy])
        col1[yy] = mis;

```

...NW

**Table 1 (cont')**

```

else if (delx >= dely[yy]) {
    coll[yy] = delx;
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
5      && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
        dx[id].jp.n[ij] = ndelx;
        dx[id].jp.x[ij] = xx;
        dx[id].score = delx;
    }
    else {
        coll[yy] = dely[yy];
        ij = dx[id].ijmp;
        if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
20      && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
            dx[id].ijmp++;
            if (++ij >= MAXJMP) {
                writejumps(id);
                ij = dx[id].ijmp = 0;
                dx[id].offset = offset;
                offset += sizeof(struct jmp) + sizeof(offset);
            }
            dx[id].jp.n[ij] = -ndely[yy];
            dx[id].jp.x[ij] = xx;
            dx[id].score = dely[yy];
        }
        if (xx == len0 && yy < len1) {
            /* last col
            */
            if (endgaps)
                coll[yy] -= ins0+ins1*(len1-yy);
            if (coll[yy] > smax) {
                smax = coll[yy];
                dmax = id;
            }
        }
        if (endgaps && xx < len0)
            coll[yy-1] -= ins0+ins1*(len0-xx);
        if (coll[yy-1] > smax) {
            smax = coll[yy-1];
            dmax = id;
        }
        tmp = col0; col0 = col1; col1 = tmp;
    }
}
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
55 (void) free((char *)col1);
}

```

Table 1 (cont')

```

/*
 *
 * print() -- only routine visible outside this module
 *
5  * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
 * nums() -- put out a number line: dumpblock()
10 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() -- put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

15 #include "nw.h"

#define SPC      3
#define P_LINE  256 /* maximum output line */
#define P_SPC    3 /* space between name or num and seq */

20 extern _day[26][26];
int olen; /* set output line length */
FILE *fx; /* output file */

25 print()
{
    int lx, ly, firstgap, lastgap; /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
30         fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
35     olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
40         pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
45         pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
50         lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
55         lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}

```

print

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
static
5 getmat(lx, ly, firstgap, lastgap)                                getmat
    int    lx, ly;                                /* "core" (minus endgaps) */
    int    firstgap, lastgap;                      /* leading trailing overlap */
{
    int    nm, i0, i1, siz0, siz1;
10    char    outx[32];
    double    pct;
    register    n0, n1;
    register char    *p0, *p1;
    /* get total matches, score
15    */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
    n0 = pp[1].spc + 1;
20    n1 = pp[0].spc + 1;
    nm = 0;
    while ( *p0 && *p1 ) {
        if (siz0) {
25            p1++;
            n1++;
            siz0--;
        }
        else if (siz1) {
30            p0++;
            n0++;
            siz1--;
        }
        else {
35            if (xbm[*p0-'A']&xbm[*p1-'A'])
                nm++;
            if (n0++ == pp[0].x[i0])
                siz0 = pp[0].n[i0++];
            if (n1++ == pp[1].x[i1])
                siz1 = pp[1].n[i1++];
40            p0++;
            p1++;
        }
    }

45    /* pct homology:
    * if penalizing endgaps, base is the shorter seq
    * else, knock off overhangs and take shorter core
    */
    if (endgaps)
50        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
    pct = 100.*((double)nm)/((double)lx);
    fprintf(fx, "\n");
55    fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
        nm, (nm == 1)? "" : "es", lx, pct);

```



Table 1 (cont')

```

fprintf(fx, "< gaps in first sequence: %d", gapx);
if (gapx) {
    (void) sprintf(outx, "(%d %s%s)",
        ngapx, (dna)? "base":"residue", (ngapx == 1)? "" : "s");
    fprintf(fx, "%s", outx);
5   fprintf(fx, ", gaps in second sequence: %d", gapy);
    if (gapy) {
        (void) sprintf(outx, "(%d %s%s)",
            ngapy, (dna)? "base":"residue", (ngapy == 1)? "" : "s");
10   fprintf(fx, "%s", outx);
    }
    if (dna)
        fprintf(fx,
15   "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
            smax, DMAT, DMIS, DINS0, DINS1);
    else
        fprintf(fx,
20   "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
            smax, PINS0, PINS1);
    if (endgaps)
        fprintf(fx,
25   "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
            firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
            lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
    else
        fprintf(fx, "<endgaps not penalized\n");
}
static      nm;          /* matches in core -- for checking */
static      lmax;        /* lengths of stripped file names */
30 static      ij[2];      /* jmp index for a path */
static      nc[2];        /* number at start of current line */
static      ni[2];        /* current elem number -- for gapping */
static      siz[2];
static char  *ps[2];      /* ptr to current element */
35 static char  *po[2];    /* ptr to next output char slot */
static char  out[2][P_LINE]; /* output line */
static char  star[P_LINE]; /* set by stars() */
/*
* print alignment of described in struct path pp[]
40 */
static
pr_align()
{
    int      nn;          /* char count */
45   int      more;
    register i;

    for (i = 0, lmax = 0; i < 2; i++) {
        nn = stripname(namex[i]);
50   if (nn > lmax)
            lmax = nn;
        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
55   ps[i] = seqx[i];
        po[i] = out[i];
    }

```

...getmat

pr\_align

Table 1 (cont')

```

5      for (nn = nm = 0, more = 1; more;) {
        for (i = more = 0; i < 2; i++) {
          /*
            * do we have more of this sequence?
            */
            if (!*ps[i])
              continue;
            more++;
            if (pp[i].spc) { /* leading space */
              *po[i]++ = ' ';
              pp[i].spc--;
            }
            else if (siz[i]) { /* in a gap */
              *po[i]++ = '-';
              siz[i]--;
            }
            else { /* we're putting a seq element
              */
              *po[i] = *ps[i];
              if (islower(*ps[i]))
                *ps[i] = toupper(*ps[i]);
              po[i]++;
              ps[i]++;
              /*
                * are we at next gap for this seq?
                */
              if (ni[i] == pp[i].x[ij[i]]) {
                /*
                  * we need to merge all gaps
                  * at this location
                  */
                siz[i] = pp[i].n[ij[i] + +];
                while (ni[i] == pp[i].x[ij[i]])
                  siz[i] += pp[i].n[ij[i] + +];
              }
              ni[i]++;
            }
          }
        }
        if (++nn == olen || !more && nn) {
          dumpblock();
          for (i = 0; i < 2; i++)
            po[i] = out[i];
          nn = 0;
        }
      }
    }
    /*
      * dump a block of lines, including numbers, stars: pr_align()
      */
    static
    dumpblock()
    {
      register i;
      for (i = 0; i < 2; i++)
        *po[i]-- = '\0';
    }
  }
}

```

...pr\_align

dumpblock

Table 1 (cont')

...dumpblock

```

5      (void) putc('\n', fx);
      for (i = 0; i < 2; i++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
              if (i == 0)
                  nums(i);
              if (i == 0 && *out[1])
                  stars();
              putline(i);
10         if (i == 0 && *out[1])
                fprintf(fx, star);
              if (i == 1)
                  nums(i);
          }
15     }
}
/*
 * put out a number line: dumpblock()
 */
20 static
nums(ix)
    int    ix;    /* index in out[] holding seq line */
{
    char    nline[P_LINE];
    register i, j;
    register char *pn, *px, *py;
    for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
        *pn = ' ';
    for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
30         if (*py == ' ' || *py == '-')
            *pn = ' ';
        else {
            if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                j = (i < 0)? -i : i;
                for (px = pn; j; j /= 10, px--)
                    *px = j%10 + '0';
                if (i < 0)
                    *px = '-';
            }
            else
                *pn = ' ';
            i++;
40         }
    }
    *pn = '\0';
    nc[ix] = i;
    for (pn = nline; *pn; pn++)
        (void) putc(*pn, fx);
50     (void) putc('\n', fx);
}
/*
 * put out a line (name, [num], seq, [num]): dumpblock()
 */
static
55 putline(ix)
    int    ix;
    {

```

nums

putline

Table 1 (cont')

...putline

```

int          i;
register char *px;

5   for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
    (void) putc(*px, fx);
    for (; i < lmax+P_SPC; i++)
        (void) putc(' ', fx);

10  /* these count from 1:
    * ni[] is current element (from 1)
    * nc[] is number at start of current line
    */
    for (px = out[ix]; *px; px++)
        (void) putc(*px&0x7F, fx);
    (void) putc('\n', fx);
}

20 /*
    * put a line of stars (seqs always in out[0], out[1]): dumpblock()
    */
static
stars()
25 {
    int          i;
    register char *p0, *p1, cx, *px;

    if (!*out[0] || (*out[0] == ' ' && *(p0[0]) == ' ') ||
        !*out[1] || (*out[1] == ' ' && *(p0[1]) == ' '))
        return;
    px = star;
    for (i = lmax+P_SPC; i; i--)
35         *px++ = ' ';

    for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
        if (isalpha(*p0) && isalpha(*p1)) {
40             if (xbm[*p0-'A']&xbm[*p1-'A']) {
                cx = '*';
                nm++;
            }
            else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
45                 cx = '.';
            else
                cx = ' ';
        }
        else
50             cx = ' ';
        *px++ = cx;
    }
    *px++ = '\n';
    *px = '\0';
55 }

```

stars

Table 1 (cont')

```

/*
 * strip path or prefix from pn, return len: pr_align()
 */
static
5 stripname(pn)                                stripname
    char    *pn;    /* file name (may be path) */
{
    register char    *px, *py;

10     py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;

    if (py)
15         (void) strcpy(pn, py);
    return(strlen(pn));
}

20

```

Table 1 (cont')

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
5  * readjumps() -- get the good jumps, from tmp file if necessary
 * writejumps() -- write a filled array of jumps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>

10 char    *jname = "/tmp/homgXXXXXXX";          /* tmp file for jumps */
FILE     *fj;
int       cleanup();                          /* cleanup tmp file */
long      lseek();

15 /*
 * remove any tmp file if we blow
 */
cleanup(i)                                     cleanup
{
    int    i;

20     {
        if (fj)
            (void) unlink(jname);
        exit(i);
    }
}

25 /*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
30 char    *
getseq(file, len)                             getseq
{
    char    *file;      /* file name */
    int     *len;       /* seq len */

35     {
        char    line[1024], *pseq;
        register char *px, *py;
        int     natgc, tlen;
        FILE     *fp;
        if ((fp = fopen(file, "r")) == 0) {
40             fprintf(stderr, "%s: can't read %s\n", prog, file);
            exit(1);
        }
        tlen = natgc = 0;
        while (fgets(line, 1024, fp)) {
45             if (*line == ';' || *line == '<' || *line == '>')
                continue;
            for (px = line; *px != '\n'; px++)
                if (isupper(*px) || islower(*px))
                    tlen++;
50         }
        if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
            fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
            exit(1);
        }
        pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
55

```

Table 1 (cont')

```

5      py = pseq + 4;
      *len = tlen;
      rewind(fp);
      while (fgets(line, 1024, fp)) {
          if (*line == ';' || *line == '<' || *line == '>')
              continue;
          for (px = line; *px != '\n'; px++) {
10              if (isupper(*px))
                  *py++ = *px;
              else if (islower(*px))
                  *py++ = toupper(*px);
              if (index("ATGCU", *(py-1)))
                  natgc++;
15          }
      }
      *py++ = '\0';
      *py = '\0';
      (void) fclose(fp);
20      dna = natgc > (tlen/3);
      return(pseq+4);
  }
  char *
  g_alloc(msg, nx, sz)
25      char *msg;          /* program, calling routine */
      int nx, sz;          /* number and size of elements */
  {
      char *px, *calloc();
      if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
30          if (*msg) {
              fprintf(stderr, "%s: g_alloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
              exit(1);
          }
      }
35      return(px);
  }

  /*
  * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
  */
40  readjmps()
  {
      int fd = -1;
      int siz, i0, i1;
45      register i, j, xx;
      if (fj) {
          (void) fclose(fj);
          if ((fd = open(jname, O_RDONLY, 0)) < 0) {
              fprintf(stderr, "%s: can't open() %s\n", prog, jname);
50              cleanup(1);
          }
      }
      for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; i++) {
55          while (1) {
              for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                  ;
          }
      }
  }

```

...getseq

g\_alloc

readjmps

Table 1 (cont')

...readjumps

```

5         if (j < 0 && dx[dmax].offset && fj) {
            (void) lseek(fd, dx[dmax].offset, 0);
            (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
            (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
            dx[dmax].ijmp = MAXJMP-1;
        }
        else
            break;
10     if (i >= JMPS) {
        fprintf(stderr, "%s: too many gaps in alignment\n", prog);
        cleanup(1);
    }
    if (j >= 0) {
15        siz = dx[dmax].jp.n[j];
        xx = dx[dmax].jp.x[j];
        dmax += siz;
        if (siz < 0) { /* gap in second seq */
            pp[1].n[i1] = -siz;
            xx += siz;
            /* id = xx - yy + len1 - 1 */
            pp[1].x[i1] = xx - dmax + len1 - 1;
            gapy++;
            ngapy -= siz;
20        /* ignore MAXGAP when doing endgaps */
            siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
            i1++;
        }
        else if (siz > 0) { /* gap in first seq */
            pp[0].n[i0] = siz;
            pp[0].x[i0] = xx;
            gapx++;
            ngapx += siz;
30        /* ignore MAXGAP when doing endgaps */
            siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
            i0++;
        }
    }
    else
        break;
40 }
/* reverse the order of jumps */
for (j = 0, i0--; j < i0; j++, i0--) {
    i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
    i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
45 }
for (j = 0, i1--; j < i1; j++, i1--) {
    i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
    i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
50 }
if (fd >= 0)
    (void) close(fd);
if (fj) {
    (void) unlink(jname);
    fj = 0;
55    offset = 0;
}
}

```



Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
5  writejumps(ix)                                     writejumps
    int    ix;
    {
        char    *mktemp();
10         if (!fj) {
            if (mktemp(jname) < 0) {
                fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
                cleanup(1);
            }
15         if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
20     }
    (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
    (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}

```

Table 2

TAT	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXXXXYYYYYY	(Length = 12 amino acids)

5      % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the TAT polypeptide) =

10      5 divided by 15 = 33.3%

Table 3

TAT	XXXXXXXXXXXX	(Length = 10 amino acids)
15      Comparison Protein	XXXXXXXXYYYYYYZZYZ	(Length = 15 amino acids)

% amino acid sequence identity =

20      (the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the TAT polypeptide) =

5 divided by 10 = 50%

Table 4

25

TAT-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLL	(Length = 16 nucleotides)

% nucleic acid sequence identity =

30

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the TAT-DNA nucleic acid sequence) =

6 divided by 14 = 42.9%

Table 5

TAT-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

5      % nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the TAT-DNA nucleic acid sequence) =

10      4 divided by 12 = 33.3%

## II.                    Compositions and Methods of the Invention

### A.                    Anti-TAT Antibodies

15      In one embodiment, the present invention provides anti-TAT antibodies which may find use herein as therapeutic and/or diagnostic agents. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

#### 1.                    Polyclonal Antibodies

20      Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen (especially when synthetic peptides are used) to a protein that is immunogenic in the species to be immunized. For example, the antigen can be conjugated to keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor, using a bifunctional or derivatizing agent, e.g., maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl<sub>2</sub>, or R<sup>1</sup>N=C=NR, where R and R<sup>1</sup> are different alkyl groups.

25      Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 µg or 5 µg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later, the animals are bled and the serum is assayed  
30      for antibody titer. Animals are boosted until the titer plateaus. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

#### 2.                    Monoclonal Antibodies

35      Monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., Nature, 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized

as described above to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. After immunization, lymphocytes are isolated and then fused with a myeloma cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)).

5       The hybridoma cells thus prepared are seeded and grown in a suitable culture medium which medium preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells (also referred to as fusion partner). For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the selective culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances  
10       prevent the growth of HGPRT-deficient cells.

      Preferred fusion partner myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a selective medium that selects against the unfused parental cells. Preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center,  
15       San Diego, California USA, and SP-2 and derivatives e.g., X63-Ag8-653 cells available from the American Type Culture Collection, Manassas, Virginia, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); and Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

20       Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

      The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis described in Munson et al., Anal. Biochem., 107:220 (1980).  
25

      Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may  
30       be grown *in vivo* as ascites tumors in an animal e.g., by i.p. injection of the cells into mice.

      The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such as, for example, affinity chromatography (e.g., using protein A or protein G-Sepharose) or ion-exchange chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, etc.

35       DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the

heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., Curr. Opin. in Immunol., 5:256-262 (1993) and Plückthun, Immunol. Revs. 130:151-188 (1992).

In a further embodiment, monoclonal antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., Nature, 348:552-554 (1990). Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., Bio/Technology, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse et al., Nuc. Acids. Res. 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The DNA that encodes the antibody may be modified to produce chimeric or fusion antibody polypeptides, for example, by substituting human heavy chain and light chain constant domain ( $C_H$  and  $C_L$ ) sequences for the homologous murine sequences (U.S. Patent No. 4,816,567; and Morrison, et al., Proc. Natl Acad. Sci. USA, 81:6851 (1984)), or by fusing the immunoglobulin coding sequence with all or part of the coding sequence for a non-immunoglobulin polypeptide (heterologous polypeptide). The non-immunoglobulin polypeptide sequences can substitute for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

### 3. Human and Humanized Antibodies

The anti-TAT antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub> or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are

those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

5 Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeven et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

15 The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity and HAMA response (human anti-mouse antibody) when the antibody is intended for human therapeutic use. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable domain sequences. The human V domain sequence which is closest to that of the rodent is identified and the human framework region (FR) within it accepted for the humanized antibody (Sims et al., J. Immunol. 151:2296 (1993); Chothia et al., J. Mol. Biol., 196:901 (1987)). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., Proc. Natl. Acad. Sci. USA, 89:4285 (1992); Presta et al., J. Immunol. 151:2623 (1993)).

25 It is further important that antibodies be humanized with retention of high binding affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

30

35

Various forms of a humanized anti-TAT antibody are contemplated. For example, the humanized antibody may be an antibody fragment, such as a Fab, which is optionally conjugated with one or more cytotoxic agent(s) in order to generate an immunoconjugate. Alternatively, the humanized antibody may be an intact antibody, such as an intact IgG1 antibody.

As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region ( $J_H$ ) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array into such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits et al., Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggemann et al., Year in Immuno. 7:33 (1993); U.S. Patent Nos. 5,545,806, 5,569,825, 5,591,669 (all of GenPharm); 5,545,807; and WO 97/17852.

Alternatively, phage display technology (McCafferty et al., Nature 348:552-553 [1990]) can be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B-cell. Phage display can be performed in a variety of formats, reviewed in, e.g., Johnson, Kevin S. and Chiswell, David J., Current Opinion in Structural Biology 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson et al., Nature, 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol. 222:581-597 (1991), or Griffith et al., EMBO J. 12:725-734 (1993). See, also, U.S. Patent Nos. 5,565,332 and 5,573,905.

As discussed above, human antibodies may also be generated by *in vitro* activated B cells (see U.S. Patents 5,567,610 and 5,229,275).

#### 4. Antibody fragments

In certain circumstances there are advantages of using antibody fragments, rather than whole antibodies. The smaller size of the fragments allows for rapid clearance, and may lead to improved access to solid tumors.

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto et al., Journal of Biochemical and Biophysical Methods 24:107-117 (1992); and Brennan et al., Science, 229:81 (1985)).

However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')<sub>2</sub> fragments (Carter et al., Bio/Technology 10:163-167 (1992)). According to another approach, F(ab')<sub>2</sub> fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')<sub>2</sub> fragment with increased in vivo half-life comprising a salvage receptor binding epitope residues are described in U.S. Patent No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; U.S. Patent No. 5,571,894; and U.S. Patent No. 5,587,458. Fv and sFv are the only species with intact combining sites that are devoid of constant regions; thus, they are suitable for reduced nonspecific binding during in vivo use. sFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an sFv. See Antibody Engineering, ed. Borrebaeck, supra. The antibody fragment may also be a "linear antibody", e.g., as described in U.S. Patent 5,641,870 for example. Such linear antibody fragments may be monospecific or bispecific.

#### 5. Bispecific Antibodies

Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of a TAT protein as described herein. Other such antibodies may combine a TAT binding site with a binding site for another protein. Alternatively, an anti-TAT arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD3), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16), so as to focus and localize cellular defense mechanisms to the TAT-expressing cell. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express TAT. These antibodies possess a TAT-binding arm and an arm which binds the cytotoxic agent (e.g., saporin, anti-interferon-α, vinca alkaloid, ricin A chain, methotrexate or radioactive isotope hapten). Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g., F(ab')<sub>2</sub> bispecific antibodies).

WO 96/16673 describes a bispecific anti-ErbB2/anti-FcγRIII antibody and U.S. Patent No. 5,837,234 discloses a bispecific anti-ErbB2/anti-FcγRI antibody. A bispecific anti-ErbB2/Fc α antibody is shown in WO98/02463. U.S. Patent No. 5,821,337 teaches a bispecific anti-ErbB2/anti-CD3 antibody.

Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., Nature 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., EMBO J. 10:3655-3659 (1991).



According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. Preferably, the fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, C<sub>H</sub>2, and C<sub>H</sub>3 regions. It is preferred to have the first heavy-chain constant region (C<sub>H</sub>1) containing the site necessary for light chain bonding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three polypeptide chains into a single expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant affect on the yield of the desired chain combination.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology 121:210 (1986).

According to another approach described in U.S. Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C<sub>H</sub>3 domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g., tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g., alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Patent No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate

F(ab')<sub>2</sub> fragments. These fragments are reduced in the presence of the dithiol complexing agent, sodium arsenite, to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Recent progress has facilitated the direct recovery of Fab'-SH fragments from *E. coli*, which can be chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.* 175: 217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')<sub>2</sub> molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., *J. Immunol.* 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a V<sub>H</sub> connected to a V<sub>L</sub> by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V<sub>H</sub> and V<sub>L</sub> domains of one fragment are forced to pair with the complementary V<sub>L</sub> and V<sub>H</sub> domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber et al., *J. Immunol.* 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

#### 6. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

#### 7. Multivalent Antibodies

A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The antibodies of the present invention can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (e.g. tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen binding sites. The preferred dimerization domain comprises (or consists of) an Fc region or a hinge region. In this scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc region. The preferred multivalent antibody herein comprises (or consists of) three to about eight, but preferably four, antigen binding sites. The multivalent antibody comprises at least one polypeptide chain (and preferably two polypeptide chains), wherein the polypeptide chain(s) comprise two or more variable domains. For instance, the polypeptide chain(s) may comprise VD1-(X1)<sub>n</sub>-VD2-(X2)<sub>n</sub>-Fc, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1. For instance, the polypeptide chain(s) may comprise: VH-CH1-flexible linker-VH-CH1-Fc region chain; or VH-CH1-VH-CH1-Fc region chain. The multivalent antibody herein preferably further comprises at least two (and preferably four) light chain variable domain polypeptides. The multivalent antibody herein may, for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further comprise a CL domain.

#### 8. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, e.g., so as to enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) of the antibody. This may be achieved by introducing one or more amino acid substitutions in an Fc region of the antibody. Alternatively or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp Med. 176:1191-1195 (1992) and Shopes, B. J. Immunol. 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff et al., Cancer Research 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design 3:219-230 (1989).

To increase the serum half life of the antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment) as described in U.S. Patent 5,739,277, for example. As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (e.g., IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, or IgG<sub>4</sub>) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

#### 9. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic

agent such as a chemotherapeutic agent, a growth inhibitory agent, a toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include <sup>212</sup>Bi, <sup>131</sup>I, <sup>131</sup>In, <sup>90</sup>Y, and <sup>186</sup>Re. Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, *Science*, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

Conjugates of an antibody and one or more small molecule toxins, such as a calicheamicin, maytansinoids, a trichothene, and CC1065, and the derivatives of these toxins that have toxin activity, are also contemplated herein.

#### Maytansine and maytansinoids

In one preferred embodiment, an anti-TAT antibody (full length or fragments) of the invention is conjugated to one or more maytansinoid molecules.

Maytansinoids are mitototic inhibitors which act by inhibiting tubulin polymerization. Maytansine was first isolated from the east African shrub *Maytenus serrata* (U.S. Patent No. 3,896,111). Subsequently, it was discovered that certain microbes also produce maytansinoids, such as maytansinol and C-3 maytansinol esters (U.S. Patent No. 4,151,042). Synthetic maytansinol and derivatives and analogues thereof are disclosed, for example, in U.S. Patent Nos. 4,137,230; 4,248,870; 4,256,746; 4,260,608; 4,265,814; 4,294,757; 4,307,016; 4,308,268; 4,308,269; 4,309,428; 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,364,866; 4,424,219; 4,450,254; 4,362,663; and 4,371,533, the disclosures of which are hereby expressly incorporated by reference.

#### Maytansinoid-antibody conjugates

In an attempt to improve their therapeutic index, maytansine and maytansinoids have been conjugated to antibodies specifically binding to tumor cell antigens. Immunoconjugates containing maytansinoids and their therapeutic use are disclosed, for example, in U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP

0 425 235 B1, the disclosures of which are hereby expressly incorporated by reference. Liu et al., Proc. Natl. Acad. Sci. USA 93:8618-8623 (1996) described immunoconjugates comprising a maytansinoid designated DM1 linked to the monoclonal antibody C242 directed against human colorectal cancer. The conjugate was found to be highly cytotoxic towards cultured colon cancer cells, and showed antitumor activity in an *in vivo* tumor growth assay. Chari et al., Cancer Research 52:127-131 (1992) describe immunoconjugates in which a  
5 maytansinoid was conjugated via a disulfide linker to the murine antibody A7 binding to an antigen on human colon cancer cell lines, or to another murine monoclonal antibody TA.1 that binds the HER-2/*neu* oncogene. The cytotoxicity of the TA.1-maytansinoid conjugate was tested *in vitro* on the human breast cancer cell line SK-BR-3, which expresses  $3 \times 10^5$  HER-2 surface antigens per cell. The drug conjugate achieved a degree of cytotoxicity similar to the free maytansinoid drug, which could be increased by increasing the number of  
10 maytansinoid molecules per antibody molecule. The A7-maytansinoid conjugate showed low systemic cytotoxicity in mice.

Anti-TAT polypeptide antibody-maytansinoid conjugates (immunoconjugates)

Anti-TAT antibody-maytansinoid conjugates are prepared by chemically linking an anti-TAT antibody to a maytansinoid molecule without significantly diminishing the biological activity of either the antibody or the  
15 maytansinoid molecule. An average of 3-4 maytansinoid molecules conjugated per antibody molecule has shown efficacy in enhancing cytotoxicity of target cells without negatively affecting the function or solubility of the antibody, although even one molecule of toxin/antibody would be expected to enhance cytotoxicity over the use of naked antibody. Maytansinoids are well known in the art and can be synthesized by known techniques or isolated from natural sources. Suitable maytansinoids are disclosed, for example, in U.S. Patent No.  
20 5,208,020 and in the other patents and nonpatent publications referred to hereinabove. Preferred maytansinoids are maytansinol and maytansinol analogues modified in the aromatic ring or at other positions of the maytansinol molecule, such as various maytansinol esters.

There are many linking groups known in the art for making antibody-maytansinoid conjugates, including, for example, those disclosed in U.S. Patent No. 5,208,020 or EP Patent 0 425 235 B1, and Chari  
25 et al., Cancer Research 52:127-131 (1992). The linking groups include disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, or esterase labile groups, as disclosed in the above-identified patents, disulfide and thioether groups being preferred.

Conjugates of the antibody and maytansinoid may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-  
30 maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). Particularly preferred coupling agents  
35 include N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP) (Carlsson et al. Biochem. J. 173:723-737 [1978]) and N-succinimidyl-4-(2-pyridyldithio)pentanoate (SPP) to provide for a disulfide linkage.

The linker may be attached to the maytansinoid molecule at various positions, depending on the type of the link. For example, an ester linkage may be formed by reaction with a hydroxyl group using conventional coupling techniques. The reaction may occur at the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with a hydroxyl group, and the C-20 position having a hydroxyl group. In a preferred embodiment, the linkage is formed at the C-3 position of maytansinol or a maytansinol analogue.

#### Calicheamicin

Another immunoconjugate of interest comprises an anti-TAT antibody conjugated to one or more calicheamicin molecules. The calicheamicin family of antibiotics are capable of producing double-stranded DNA breaks at sub-picomolar concentrations. For the preparation of conjugates of the calicheamicin family, see U.S. patents 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, 5,877,296 (all to American Cyanamid Company). Structural analogues of calicheamicin which may be used include, but are not limited to,  $\gamma_1^I$ ,  $\alpha_2^I$ ,  $\alpha_3^I$ , N-acetyl- $\gamma_1^I$ , PSAG and  $\theta_1^I$  (Hinman et al., Cancer Research 53:3336-3342 (1993), Lode et al., Cancer Research 58:2925-2928 (1998) and the aforementioned U.S. patents to American Cyanamid). Another anti-tumor drug that the antibody can be conjugated is QFA which is an antifolate. Both calicheamicin and QFA have intracellular sites of action and do not readily cross the plasma membrane. Therefore, cellular uptake of these agents through antibody mediated internalization greatly enhances their cytotoxic effects.

#### Other cytotoxic agents

Other antitumor agents that can be conjugated to the anti-TAT antibodies of the invention include BCNU, streptozocin, vincristine and 5-fluorouracil, the family of agents known collectively LL-E33288 complex described in U.S. patents 5,053,394, 5,770,710, as well as esperamicins (U.S. patent 5,877,296).

Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, WO 93/21232 published October 28, 1993.

The present invention further contemplates an immunoconjugate formed between an antibody and a compound with nucleolytic activity (e.g., a ribonuclease or a DNA endonuclease such as a deoxyribonuclease; DNase).

For selective destruction of the tumor, the antibody may comprise a highly radioactive atom. A variety of radioactive isotopes are available for the production of radioconjugated anti-TAT antibodies. Examples include  $\text{At}^{211}$ ,  $\text{I}^{131}$ ,  $\text{I}^{125}$ ,  $\text{Y}^{90}$ ,  $\text{Re}^{186}$ ,  $\text{Re}^{188}$ ,  $\text{Sm}^{153}$ ,  $\text{Bi}^{212}$ ,  $\text{P}^{32}$ ,  $\text{Pb}^{212}$  and radioactive isotopes of Lu. When the conjugate is used for diagnosis, it may comprise a radioactive atom for scintigraphic studies, for example  $\text{tc}^{99\text{m}}$  or  $\text{I}^{123}$ , or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance

imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

The radio- or other labels may be incorporated in the conjugate in known ways. For example, the peptide may be biosynthesized or may be synthesized by chemical amino acid synthesis using suitable amino acid precursors involving, for example, fluorine-19 in place of hydrogen. Labels such as  $^{99m}\text{Tc}$  or  $^{123}\text{I}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$  and  $^{111}\text{In}$  can be attached via a cysteine residue in the peptide. Yttrium-90 can be attached via a lysine residue. The IODOGEN method (Fraker et al (1978) Biochem. Biophys. Res. Commun. 80: 49-57 can be used to incorporate iodine-123. "Monoclonal Antibodies in Immunoscintigraphy" (Chatal, CRC Press 1989) describes other methods in detail.

Conjugates of the antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science* 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of the cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., *Cancer Research* 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

Alternatively, a fusion protein comprising the anti-TAT antibody and cytotoxic agent may be made, e.g., by recombinant techniques or peptide synthesis. The length of DNA may comprise respective regions encoding the two portions of the conjugate either adjacent one another or separated by a region encoding a linker peptide which does not destroy the desired properties of the conjugate.

In yet another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pre-targeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) which is conjugated to a cytotoxic agent (e.g., a radionucleotide).

#### 10. Immunoliposomes

The anti-TAT antibodies disclosed herein may also be formulated as immunoliposomes. A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., *Proc. Natl. Acad. Sci. USA* 82:3688 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA* 77:4030 (1980); U.S. Pat. Nos. 4,485,045 and 4,544,545;

and WO97/38731 published October 23, 1997. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., *J. Biol. Chem.* 257:286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon et al., *J. National Cancer Inst.* 81(19):1484 (1989).

#### B. TAT Binding Oligopeptides

TAT binding oligopeptides of the present invention are oligopeptides that bind, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be chemically synthesized using known oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. TAT binding oligopeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such oligopeptides that are capable of binding, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in the art (see, e.g., U.S. Patent Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 81:3998-4002 (1984); Geysen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 82:178-182 (1985); Geysen et al., in *Synthetic Peptides as Antigens*, 130-149 (1986); Geysen et al., *J. Immunol. Meth.*, 102:259-274 (1987); Schoofs et al., *J. Immunol.*, 140:611-616 (1988), Cwirla, S. E. et al. (1990) *Proc. Natl. Acad. Sci. USA*, 87:6378; Lowman, H.B. et al. (1991) *Biochemistry*, 30:10832; Clackson, T. et al. (1991) *Nature*, 352: 624; Marks, J. D. et al. (1991), *J. Mol. Biol.*, 222:581; Kang, A.S. et al. (1991) *Proc. Natl. Acad. Sci. USA*, 88:8363, and Smith, G. P. (1991) *Current Opin. Biotechnol.*, 2:668).

In this regard, bacteriophage (phage) display is one well known technique which allows one to screen large oligopeptide libraries to identify member(s) of those libraries which are capable of specifically binding to a polypeptide target. Phage display is a technique by which variant polypeptides are displayed as fusion proteins to the coat protein on the surface of bacteriophage particles (Scott, J.K. and Smith, G. P. (1990) *Science* 249: 386). The utility of phage display lies in the fact that large libraries of selectively randomized protein variants (or randomly cloned cDNAs) can be rapidly and efficiently sorted for those sequences that bind to a target molecule with high affinity. Display of peptide (Cwirla, S. E. et al. (1990) *Proc. Natl. Acad. Sci.*



USA, 87:6378) or protein (Lowman, H.B. et al. (1991) Biochemistry, 30:10832; Clackson, T. et al. (1991) Nature, 352: 624; Marks, J. D. et al. (1991), J. Mol. Biol., 222:581; Kang, A.S. et al. (1991) Proc. Natl. Acad. Sci. USA, 88:8363) libraries on phage have been used for screening millions of polypeptides or oligopeptides for ones with specific binding properties (Smith, G. P. (1991) Current Opin. Biotechnol., 2:668). Sorting phage libraries of random mutants requires a strategy for constructing and propagating a large number of variants, a procedure for affinity purification using the target receptor, and a means of evaluating the results of binding enrichments. U.S. Patent Nos. 5,223,409, 5,403,484, 5,571,689, and 5,663,143.

Although most phage display methods have used filamentous phage, lambdoid phage display systems (WO 95/34683; U.S. 5,627,024), T4 phage display systems (Ren, Z-J. et al. (1998) Gene 215:439; Zhu, Z. (1997) CAN 33:534; Jiang, J. et al. (1997) can 128:44380; Ren, Z-J. et al. (1997) CAN 127:215644; Ren, Z-J. (1996) Protein Sci. 5:1833; Efimov, V. P. et al. (1995) Virus Genes 10:173) and T7 phage display systems (Smith, G. P. and Scott, J.K. (1993) Methods in Enzymology, 217, 228-257; U.S. 5,766,905) are also known.

Many other improvements and variations of the basic phage display concept have now been developed. These improvements enhance the ability of display systems to screen peptide libraries for binding to selected target molecules and to display functional proteins with the potential of screening these proteins for desired properties. Combinatorial reaction devices for phage display reactions have been developed (WO 98/14277) and phage display libraries have been used to analyze and control bimolecular interactions (WO 98/20169; WO 98/20159) and properties of constrained helical peptides (WO 98/20036). WO 97/35196 describes a method of isolating an affinity ligand in which a phage display library is contacted with one solution in which the ligand will bind to a target molecule and a second solution in which the affinity ligand will not bind to the target molecule, to selectively isolate binding ligands. WO 97/46251 describes a method of biopanning a random phage display library with an affinity purified antibody and then isolating binding phage, followed by a micropanning process using microplate wells to isolate high affinity binding phage. The use of *Staphylococcus aureus* protein A as an affinity tag has also been reported (Li et al. (1998) Mol Biotech., 9:187). WO 97/47314 describes the use of substrate subtraction libraries to distinguish enzyme specificities using a combinatorial library which may be a phage display library. A method for selecting enzymes suitable for use in detergents using phage display is described in WO 97/09446. Additional methods of selecting specific binding proteins are described in U.S. Patent Nos. 5,498,538, 5,432,018, and WO 98/15833.

Methods of generating peptide libraries and screening these libraries are also disclosed in U.S. Patent Nos. 5,723,286, 5,432,018, 5,580,717, 5,427,908, 5,498,530, 5,770,434, 5,734,018, 5,698,426, 5,763,192, and 5,723,323.

### C. TAT Binding Organic Molecules

TAT binding organic molecules are organic molecules other than oligopeptides or antibodies as defined herein that bind, preferably specifically, to a TAT polypeptide as described herein. TAT binding organic molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). TAT binding organic molecules are usually less than about 2000 daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 daltons in size, wherein such organic molecules

that are capable of binding, preferably specifically, to a TAT polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). TAT binding organic molecules may be, for example, aldehydes, ketones, oximes, hydrazones, semicarbazones, carbazides, primary amines, secondary amines, tertiary amines, N-substituted hydrazines, hydrazides, alcohols, ethers, thiols, thioethers, disulfides, carboxylic acids, esters, amides, ureas, carbamates, carbonates, ketals, thioketals, acetals, thioacetals, aryl halides, aryl sulfonates, alkyl halides, alkyl sulfonates, aromatic compounds, heterocyclic compounds, anilines, alkenes, alkynes, diols, amino alcohols, oxazolidines, oxazolines, thiazolidines, thiazolines, enamines, sulfonamides, epoxides, aziridines, isocyanates, sulfonyl chlorides, diazo compounds, acid chlorides, or the like.

D. Screening for Anti-TAT Antibodies, TAT Binding Oligopeptides and TAT Binding Organic Molecules With the Desired Properties

Techniques for generating antibodies, oligopeptides and organic molecules that bind to TAT polypeptides have been described above. One may further select antibodies, oligopeptides or other organic molecules with certain biological characteristics, as desired.

The growth inhibitory effects of an anti-TAT antibody, oligopeptide or other organic molecule of the invention may be assessed by methods known in the art, e.g., using cells which express a TAT polypeptide either endogenously or following transfection with the TAT gene. For example, appropriate tumor cell lines and TAT-transfected cells may be treated with an anti-TAT monoclonal antibody, oligopeptide or other organic molecule of the invention at various concentrations for a few days (e.g., 2-7) days and stained with crystal violet or MTT or analyzed by some other colorimetric assay. Another method of measuring proliferation would be by comparing <sup>3</sup>H-thymidine uptake by the cells treated in the presence or absence of an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule of the invention. After treatment, the cells are harvested and the amount of radioactivity incorporated into the DNA quantitated in a scintillation counter. Appropriate positive controls include treatment of a selected cell line with a growth inhibitory antibody known to inhibit growth of that cell line. Growth inhibition of tumor cells *in vivo* can be determined in various ways known in the art. Preferably, the tumor cell is one that overexpresses a TAT polypeptide. Preferably, the anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule will inhibit cell proliferation of a TAT-expressing tumor cell *in vitro* or *in vivo* by about 25-100% compared to the untreated tumor cell, more preferably, by about 30-100%, and even more preferably by about 50-100% or 70-100%, in one embodiment, at an antibody concentration of about 0.5 to 30 µg/ml. Growth inhibition can be measured at an antibody concentration of about 0.5 to 30 µg/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the antibody. The antibody is growth inhibitory *in vivo* if administration of the anti-TAT antibody at about 1 µg/kg to about 100 mg/kg body weight results in reduction in tumor size or reduction of tumor cell proliferation within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

To select for an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule which induces cell death, loss of membrane integrity as indicated by, e.g., propidium iodide (PI), trypan blue or 7AAD uptake may be assessed relative to control. A PI uptake assay can be performed in the absence of complement and immune effector cells. TAT polypeptide-expressing tumor cells are incubated with medium alone or medium containing the appropriate anti-TAT antibody (e.g., at about 10 µg/ml), TAT binding oligopeptide or TAT binding organic molecule. The cells are incubated for a 3 day time period. Following each treatment, cells are washed and aliquoted into 35 mm strainer-capped 12 x 75 tubes (1ml per tube, 3 tubes per treatment group) for removal of cell clumps. Tubes then receive PI (10 µg/ml). Samples may be analyzed using a FACSCAN® flow cytometer and FACSCONVERT® CellQuest software (Becton Dickinson). Those anti-TAT antibodies, TAT binding oligopeptides or TAT binding organic molecules that induce statistically significant levels of cell death as determined by PI uptake may be selected as cell death-inducing anti-TAT antibodies, TAT binding oligopeptides or TAT binding organic molecules.

To screen for antibodies, oligopeptides or other organic molecules which bind to an epitope on a TAT polypeptide bound by an antibody of interest, a routine cross-blocking assay such as that described in Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. This assay can be used to determine if a test antibody, oligopeptide or other organic molecule binds the same site or epitope as a known anti-TAT antibody. Alternatively, or additionally, epitope mapping can be performed by methods known in the art. For example, the antibody sequence can be mutagenized such as by alanine scanning, to identify contact residues. The mutant antibody is initially tested for binding with polyclonal antibody to ensure proper folding. In a different method, peptides corresponding to different regions of a TAT polypeptide can be used in competition assays with the test antibodies or with a test antibody and an antibody with a characterized or known epitope.

#### E. Antibody Dependent Enzyme Mediated Prodrug Therapy (ADEPT)

The antibodies of the present invention may also be used in ADEPT by conjugating the antibody to a prodrug-activating enzyme which converts a prodrug (e.g., a peptidyl chemotherapeutic agent, see WO81/01145) to an active anti-cancer drug. See, for example, WO 88/07378 and U.S. Patent No. 4,975,278.

The enzyme component of the immunoconjugate useful for ADEPT includes any enzyme capable of acting on a prodrug in such a way so as to convert it into its more active, cytotoxic form.

Enzymes that are useful in the method of this invention include, but are not limited to, alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratia protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypeptidases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as β-galactosidase and neuraminidase useful for converting glycosylated prodrugs into free drugs; β-lactamase useful for converting drugs derivatized with β-lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful

for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes", can be used to convert the prodrugs of the invention into free active drugs (see, e.g., Massey, Nature 328:457-458 (1987)). Antibody-abzyme conjugates can be prepared as described herein for delivery of the abzyme to a tumor cell population.

5           The enzymes of this invention can be covalently bound to the anti-TAT antibodies by techniques well known in the art such as the use of the heterobifunctional crosslinking reagents discussed above. Alternatively, fusion proteins comprising at least the antigen binding region of an antibody of the invention linked to at least a functionally active portion of an enzyme of the invention can be constructed using recombinant DNA techniques well known in the art (see, e.g., Neuberger et al., Nature 312:604-608 (1984)).

10           F.       Full-Length TAT Polypeptides

The present invention also provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as TAT polypeptides. In particular, cDNAs (partial and full-length) encoding various TAT polypeptides have been identified and isolated, as disclosed in further detail in the Examples below.

15           As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the TAT polypeptides and encoding nucleic acids described herein, in some cases, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

20           G.       Anti-TAT Antibody and TAT Polypeptide Variants

In addition to the anti-TAT antibodies and full-length native sequence TAT polypeptides described herein, it is contemplated that anti-TAT antibody and TAT polypeptide variants can be prepared. Anti-TAT antibody and TAT polypeptide variants can be prepared by introducing appropriate nucleotide changes into the encoding DNA, and/or by synthesis of the desired antibody or polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the anti-TAT antibody or TAT polypeptide, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

30           Variations in the anti-TAT antibodies and TAT polypeptides described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the antibody or polypeptide that results in a change in the amino acid sequence as compared with the native sequence antibody or polypeptide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the anti-TAT antibody or TAT polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the anti-TAT antibody or

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TAT polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

Anti-TAT antibody and TAT polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native antibody or protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the anti-TAT antibody or TAT polypeptide.

Anti-TAT antibody and TAT polypeptide fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating antibody or polypeptide fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired antibody or polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, anti-TAT antibody and TAT polypeptide fragments share at least one biological and/or immunological activity with the native anti-TAT antibody or TAT polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

	Original Residue	Exemplary Substitutions	Preferred Substitutions
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
10	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe; norleucine	leu
15	Leu (L)	norleucine; ile; val; met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
20	Ser (S)	thr	thr
	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe; ala; norleucine	leu

- Substantial modifications in function or immunological identity of the anti-TAT antibody or TAT polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining
- 30 (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:
- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- 35 (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain-orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

- Non-conservative substitutions will entail exchanging a member of one of these classes for another
- 40 class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al. Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the anti-TAT antibody or TAT polypeptide variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244:1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

Any cysteine residue not involved in maintaining the proper conformation of the anti-TAT antibody or TAT polypeptide also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the anti-TAT antibody or TAT polypeptide to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (e.g., 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and human TAT polypeptide. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Nucleic acid molecules encoding amino acid sequence variants of the anti-TAT antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-

mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-TAT antibody.

#### H. Modifications of Anti-TAT Antibodies and TAT Polypeptides

Covalent modifications of anti-TAT antibodies and TAT polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of an anti-TAT antibody or TAT polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the anti-TAT antibody or TAT polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking anti-TAT antibody or TAT polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-TAT antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the  $\alpha$ -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the anti-TAT antibody or TAT polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the antibody or polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence anti-TAT antibody or TAT polypeptide (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence anti-TAT antibody or TAT polypeptide. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Glycosylation of antibodies and other polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylglactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.



Addition of glycosylation sites to the anti-TAT antibody or TAT polypeptide is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original anti-TAT antibody or TAT polypeptide (for O-linked glycosylation sites). The anti-TAT antibody or TAT polypeptide amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the anti-TAT antibody or TAT polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the anti-TAT antibody or TAT polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the anti-TAT antibody or TAT polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of anti-TAT antibody or TAT polypeptide comprises linking the antibody or polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. The antibody or polypeptide also may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules), or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Oslo, A., Ed., (1980).

The anti-TAT antibody or TAT polypeptide of the present invention may also be modified in a way to form chimeric molecules comprising an anti-TAT antibody or TAT polypeptide fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the anti-TAT antibody or TAT polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the anti-TAT antibody or TAT polypeptide. The presence of such epitope-tagged forms of the anti-TAT antibody or TAT polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the anti-TAT

antibody or TAT polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an  $\alpha$ -tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the anti-TAT antibody or TAT polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of an anti-TAT antibody or TAT polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH<sub>2</sub> and CH<sub>3</sub>, or the hinge, CH<sub>1</sub>, CH<sub>2</sub> and CH<sub>3</sub> regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

#### I. Preparation of Anti-TAT Antibodies and TAT Polypeptides

The description below relates primarily to production of anti-TAT antibodies and TAT polypeptides by culturing cells transformed or transfected with a vector containing anti-TAT antibody- and TAT polypeptide-encoding nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare anti-TAT antibodies and TAT polypeptides. For instance, the appropriate amino acid sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the anti-TAT antibody or TAT polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the desired anti-TAT antibody or TAT polypeptide.

##### 1. Isolation of DNA Encoding Anti-TAT Antibody or TAT Polypeptide

DNA encoding anti-TAT antibody or TAT polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the anti-TAT antibody or TAT polypeptide mRNA and to express it at a detectable level. Accordingly, human anti-TAT antibody or TAT polypeptide DNA can be conveniently obtained from a cDNA library prepared from human tissue. The anti-TAT antibody- or TAT polypeptide-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated

nucleic acid synthesis).

Libraries can be screened with probes (such as oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding anti-TAT antibody or TAT polypeptide is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

Techniques for screening a cDNA library are well known in the art. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like <sup>32</sup>P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

## 2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for anti-TAT antibody or TAT polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl<sub>2</sub>, CaPO<sub>4</sub>, liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology,

52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan'*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

Full length antibody, antibody fragments, and antibody fusion proteins can be produced in bacteria, in particular when glycosylation and Fc effector function are not needed, such as when the therapeutic antibody is conjugated to a cytotoxic agent (e.g., a toxin) and the immunoconjugate by itself shows effectiveness in tumor cell destruction. Full length antibodies have greater half life in circulation. Production in *E. coli* is faster and more cost efficient. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. 5,648,237 (Carter et al.), U.S. 5,789,199 (Joly et al.), and U.S. 5,840,523 (Simmons et al.) which describes translation initiation regio (TIR) and signal sequences for optimizing expression and secretion, these patents incorporated herein by reference. After expression, the antibody is isolated from the *E. coli* cell paste in a soluble fraction and can be purified through, e.g., a protein A or G column depending on the isotype. Final purification can be carried out similar to the process for purifying antibody expressed e.g., in CHO cells.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for anti-TAT antibody- or TAT polypeptide-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesei* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylotrophic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of glycosylated anti-TAT antibody or TAT polypeptide are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells, such as cell cultures of cotton, corn, potato, soybean, petunia, tomato, and tobacco. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for transfection of *Spodoptera frugiperda* cells.

However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen. Virol. 36:59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary cells/-DHFR (CHO, Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod. 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2,

HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., Annals N.Y. Acad. Sci. 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

Host cells are transformed with the above-described expression or cloning vectors for anti-TAT antibody or TAT polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

### 3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding anti-TAT antibody or TAT polypeptide may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The TAT may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the anti-TAT antibody- or TAT polypeptide-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces*  $\alpha$ -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 $\mu$  plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification

of cells competent to take up the anti-TAT antibody- or TAT polypeptide-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the anti-TAT antibody- or TAT polypeptide-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the  $\beta$ -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the *tac* promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding anti-TAT antibody or TAT polypeptide.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

Anti-TAT antibody or TAT polypeptide transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the anti-TAT antibody or TAT polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin,  $\alpha$ -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the

late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the anti-TAT antibody or TAT polypeptide coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding anti-TAT antibody or TAT polypeptide.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of anti-TAT antibody or TAT polypeptide in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

#### 4. Culturing the Host Cells

The host cells used to produce the anti-TAT antibody or TAT polypeptide of this invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham et al Meth. Enz. 58:44 (1979), Barnes et al., Anal. Biochem. 102:255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Patent Re. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as GENTAMYCIN™ drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.



#### 5. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence TAT polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to TAT DNA and encoding a specific antibody epitope.

#### 6. Purification of Anti-TAT Antibody and TAT Polypeptide

Forms of anti-TAT antibody and TAT polypeptide may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of anti-TAT antibody and TAT polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify anti-TAT antibody and TAT polypeptide from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the anti-TAT antibody and TAT polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular anti-TAT antibody or TAT polypeptide produced.

When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Carter et al., Bio/Technology 10:163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium

acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human  $\gamma 1$ ,  $\gamma 2$  or  $\gamma 4$  heavy chains (Lindmark et al., *J. Immunol. Meth.* 62:1-13 (1983)). Protein G is recommended for all mouse isotypes and for human  $\gamma 3$  (Guss et al., *EMBO J.* 5:15671575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a  $C_{H3}$  domain, the Bakerbond ABX<sup>™</sup> resin (J. T. Baker, Phillipsburg, NJ) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE<sup>™</sup> chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5-4.5, preferably performed at low salt concentrations (e.g., from about 0-0.25M salt).

#### J. Pharmaceutical Formulations

Therapeutic formulations of the anti-TAT antibodies, TAT binding oligopeptides, TAT binding organic molecules and/or TAT polypeptides used in accordance with the present invention are prepared for storage by mixing the antibody, polypeptide, oligopeptide or organic molecule having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as acetate, Tris, phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine,

histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; tonicifiers such as trehalose and sodium chloride; sugars such as sucrose, mannitol, trehalose or sorbitol; surfactant such as polysorbate; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG). The antibody preferably comprises the antibody at a concentration of between 5-200 mg/ml, preferably between 10-100 mg/ml.

The formulations herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, in addition to an anti-TAT antibody, TAT binding oligopeptide, or TAT binding organic molecule, it may be desirable to include in the one formulation, an additional antibody, e.g., a second anti-TAT antibody which binds a different epitope on the TAT polypeptide, or an antibody to some other target such as a growth factor that affects the growth of the particular cancer. Alternatively, or additionally, the composition may further comprise a chemotherapeutic agent, cytotoxic agent, cytokine, growth inhibitory agent, anti-hormonal agent, and/or cardioprotectant. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and  $\gamma$  ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT® (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

K. Diagnosis and Treatment with Anti-TAT Antibodies, TAT Binding Oligopeptides and TAT Binding Organic Molecules

To determine TAT expression in the cancer, various diagnostic assays are available. In one embodiment, TAT polypeptide overexpression may be analyzed by immunohistochemistry (IHC). Paraffin embedded tissue sections from a tumor biopsy may be subjected to the IHC assay and accorded a TAT protein staining intensity criteria as follows:

Score 0 - no staining is observed or membrane staining is observed in less than 10% of tumor cells.

Score 1+ - a faint/barely perceptible membrane staining is detected in more than 10% of the tumor cells. The cells are only stained in part of their membrane.

Score 2+ - a weak to moderate complete membrane staining is observed in more than 10% of the tumor cells.

Score 3+ - a moderate to strong complete membrane staining is observed in more than 10% of the tumor cells.

Those tumors with 0 or 1+ scores for TAT polypeptide expression may be characterized as not overexpressing TAT, whereas those tumors with 2+ or 3+ scores may be characterized as overexpressing TAT.

Alternatively, or additionally, FISH assays such as the INFORM® (sold by Ventana, Arizona) or PATHVISION® (Vysis, Illinois) may be carried out on formalin-fixed, paraffin-embedded tumor tissue to determine the extent (if any) of TAT overexpression in the tumor.

TAT overexpression or amplification may be evaluated using an *in vivo* diagnostic assay, e.g., by administering a molecule (such as an antibody, oligopeptide or organic molecule) which binds the molecule to be detected and is tagged with a detectable label (e.g., a radioactive isotope or a fluorescent label) and externally scanning the patient for localization of the label.

As described above, the anti-TAT antibodies, oligopeptides and organic molecules of the invention have various non-therapeutic applications. The anti-TAT antibodies, oligopeptides and organic molecules of the present invention can be useful for diagnosis and staging of TAT polypeptide-expressing cancers (e.g., in radioimaging). The antibodies, oligopeptides and organic molecules are also useful for purification or immunoprecipitation of TAT polypeptide from cells, for detection and quantitation of TAT polypeptide *in vitro*, e.g., in an ELISA or a Western blot, to kill and eliminate TAT-expressing cells from a population of mixed cells as a step in the purification of other cells.

Currently, depending on the stage of the cancer, cancer treatment involves one or a combination of the following therapies: surgery to remove the cancerous tissue, radiation therapy, and chemotherapy. Anti-TAT antibody, oligopeptide or organic molecule therapy may be especially desirable in elderly patients who do not tolerate the toxicity and side effects of chemotherapy well and in metastatic disease where radiation therapy has limited usefulness. The tumor targeting anti-TAT antibodies, oligopeptides and organic molecules of the invention are useful to alleviate TAT-expressing cancers upon initial diagnosis of the disease or during relapse. For therapeutic applications, the anti-TAT antibody, oligopeptide or organic molecule can be used alone, or in combination therapy with, e.g., hormones, antiangiogens, or radiolabelled compounds, or with surgery, cryotherapy, and/or radiotherapy. Anti-TAT antibody, oligopeptide or organic molecule treatment can be administered in conjunction with other forms of conventional therapy, either consecutively with, pre- or post-conventional therapy. Chemotherapeutic drugs such as TAXOTERE® (docetaxel), TAXOL® (paclitaxel), estramustine and mitoxantrone are used in treating cancer, in particular, in good risk patients. In the present method of the invention for treating or alleviating cancer, the cancer patient can be administered anti-TAT

antibody, oligopeptide or organic molecule in conjunction with treatment with the one or more of the preceding chemotherapeutic agents. In particular, combination therapy with paclitaxel and modified derivatives (see, e.g., EP0600517) is contemplated. The anti-TAT antibody, oligopeptide or organic molecule will be administered with a therapeutically effective dose of the chemotherapeutic agent. In another embodiment, the anti-TAT antibody, oligopeptide or organic molecule is administered in conjunction with chemotherapy to enhance the activity and efficacy of the chemotherapeutic agent, e.g., paclitaxel. The Physicians' Desk Reference (PDR) discloses dosages of these agents that have been used in treatment of various cancers. The dosing regimen and dosages of these aforementioned chemotherapeutic drugs that are therapeutically effective will depend on the particular cancer being treated, the extent of the disease and other factors familiar to the physician of skill in the art and can be determined by the physician.

In one particular embodiment, a conjugate comprising an anti-TAT antibody, oligopeptide or organic molecule conjugated with a cytotoxic agent is administered to the patient. Preferably, the immunoconjugate bound to the TAT protein is internalized by the cell, resulting in increased therapeutic efficacy of the immunoconjugate in killing the cancer cell to which it binds. In a preferred embodiment, the cytotoxic agent targets or interferes with the nucleic acid in the cancer cell. Examples of such cytotoxic agents are described above and include maytansinoids, calicheamicins, ribonucleases and DNA endonucleases.

The anti-TAT antibodies, oligopeptides, organic molecules or toxin conjugates thereof are administered to a human patient, in accord with known methods, such as intravenous administration, e.g., as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous or subcutaneous administration of the antibody, oligopeptide or organic molecule is preferred.

Other therapeutic regimens may be combined with the administration of the anti-TAT antibody, oligopeptide or organic molecule. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Preferably such combined therapy results in a synergistic therapeutic effect.

It may also be desirable to combine administration of the anti-TAT antibody or antibodies, oligopeptides or organic molecules, with administration of an antibody directed against another tumor antigen associated with the particular cancer.

In another embodiment, the therapeutic treatment methods of the present invention involves the combined administration of an anti-TAT antibody (or antibodies), oligopeptides or organic molecules and one or more chemotherapeutic agents or growth inhibitory agents, including co-administration of cocktails of different chemotherapeutic agents. Chemotherapeutic agents include estramustine phosphate, prednimustine, cisplatin, 5-fluorouracil, melphalan, cyclophosphamide, hydroxyurea and hydroxyureataxanes (such as paclitaxel and doxorubicin) and/or anthracycline antibiotics. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy

Service Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992).

The antibody, oligopeptide or organic molecule may be combined with an anti-hormonal compound; e.g., an anti-estrogen compound such as tamoxifen; an anti-progesterone such as onapristone (see, EP 616 812); or an anti-androgen such as flutamide, in dosages known for such molecules. Where the cancer to be treated is androgen independent cancer, the patient may previously have been subjected to anti-androgen therapy and, after the cancer becomes androgen independent, the anti-TAT antibody, oligopeptide or organic molecule (and optionally other agents as described herein) may be administered to the patient.

Sometimes, it may be beneficial to also co-administer a cardioprotectant (to prevent or reduce myocardial dysfunction associated with the therapy) or one or more cytokines to the patient. In addition to the above therapeutic regimes, the patient may be subjected to surgical removal of cancer cells and/or radiation therapy, before, simultaneously with, or post antibody, oligopeptide or organic molecule therapy. Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the agent and anti-TAT antibody, oligopeptide or organic molecule.

For the prevention or treatment of disease, the dosage and mode of administration will be chosen by the physician according to known criteria. The appropriate dosage of antibody, oligopeptide or organic molecule will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the antibody, oligopeptide or organic molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, oligopeptide or organic molecule, and the discretion of the attending physician. The antibody, oligopeptide or organic molecule is suitably administered to the patient at one time or over a series of treatments. Preferably, the antibody, oligopeptide or organic molecule is administered by intravenous infusion or by subcutaneous injections. Depending on the type and severity of the disease, about 1 µg/kg to about 50 mg/kg body weight (e.g., about 0.1-15mg/kg/dose) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A dosing regimen can comprise administering an initial loading dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg/kg of the anti-TAT antibody. However, other dosage regimens may be useful. A typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. The progress of this therapy can be readily monitored by conventional methods and assays and based on criteria known to the physician or other persons of skill in the art.

Aside from administration of the antibody protein to the patient, the present application contemplates administration of the antibody by gene therapy. Such administration of nucleic acid encoding the antibody is encompassed by the expression "administering a therapeutically effective amount of an antibody". See, for example, WO96/07321 published March 14, 1996 concerning the use of gene therapy to generate intracellular antibodies.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells; *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient,

usually at the site where the antibody is required. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes which are implanted into the patient (see, e.g., U.S. Patent Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. A commonly used vector for *ex vivo* delivery of the gene is a retroviral vector.

The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral vectors (such as adenovirus, Herpes simplex I virus, or adeno-associated virus) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are DOTMA, DOPE and DC-Chol, for example). For review of the currently known gene marking and gene therapy protocols see Anderson et al., *Science* 256:808-813 (1992). See also WO 93/25673 and the references cited therein.

The anti-TAT antibodies of the invention can be in the different forms encompassed by the definition of "antibody" herein. Thus, the antibodies include full length or intact antibody, antibody fragments, native sequence antibody or amino acid variants, humanized, chimeric or fusion antibodies, immunoconjugates, and functional fragments thereof. In fusion antibodies an antibody sequence is fused to a heterologous polypeptide sequence. The antibodies can be modified in the Fc region to provide desired effector functions. As discussed in more detail in the sections herein, with the appropriate Fc regions, the naked antibody bound on the cell surface can induce cytotoxicity, e.g., via antibody-dependent cellular cytotoxicity (ADCC) or by recruiting complement in complement dependent cytotoxicity, or some other mechanism. Alternatively, where it is desirable to eliminate or reduce effector function, so as to minimize side effects or therapeutic complications, certain other Fc regions may be used.

In one embodiment, the antibody competes for binding or bind substantially to, the same epitope as the antibodies of the invention. Antibodies having the biological characteristics of the present anti-TAT antibodies of the invention are also contemplated, specifically including the *in vivo* tumor targeting and any cell proliferation inhibition or cytotoxic characteristics.

Methods of producing the above antibodies are described in detail herein.

The present anti-TAT antibodies, oligopeptides and organic molecules are useful for treating a TAT-expressing cancer or alleviating one or more symptoms of the cancer in a mammal. Such a cancer includes prostate cancer, cancer of the urinary tract, lung cancer, breast cancer, colon cancer and ovarian cancer, more specifically, prostate adenocarcinoma, renal cell carcinomas, colorectal adenocarcinomas, lung adenocarcinomas, lung squamous cell carcinomas, and pleural mesothelioma. The cancers encompass metastatic cancers of any of the preceding. The antibody, oligopeptide or organic molecule is able to bind to at least a portion of the cancer cells that express TAT polypeptide in the mammal. In a preferred embodiment, the antibody, oligopeptide or organic molecule is effective to destroy or kill TAT-expressing tumor cells or inhibit

the growth of such tumor cells, *in vitro* or *in vivo*, upon binding to TAT polypeptide on the cell. Such an antibody includes a naked anti-TAT antibody (not conjugated to any agent). Naked antibodies that have cytotoxic or cell growth inhibition properties can be further harnessed with a cytotoxic agent to render them even more potent in tumor cell destruction. Cytotoxic properties can be conferred to an anti-TAT antibody by, e.g., conjugating the antibody with a cytotoxic agent, to form an immunoconjugate as described herein. The cytotoxic agent or a growth inhibitory agent is preferably a small molecule. Toxins such as calicheamicin or a maytansinoid and analogs or derivatives thereof, are preferable.

The invention provides a composition comprising an anti-TAT antibody, oligopeptide or organic molecule of the invention, and a carrier. For the purposes of treating cancer, compositions can be administered to the patient in need of such treatment, wherein the composition can comprise one or more anti-TAT antibodies present as an immunoconjugate or as the naked antibody. In a further embodiment, the compositions can comprise these antibodies, oligopeptides or organic molecules in combination with other therapeutic agents such as cytotoxic or growth inhibitory agents, including chemotherapeutic agents. The invention also provides formulations comprising an anti-TAT antibody, oligopeptide or organic molecule of the invention, and a carrier. In one embodiment, the formulation is a therapeutic formulation comprising a pharmaceutically acceptable carrier.

Another aspect of the invention is isolated nucleic acids encoding the anti-TAT antibodies. Nucleic acids encoding both the H and L chains and especially the hypervariable region residues, chains which encode the native sequence antibody as well as variants, modifications and humanized versions of the antibody, are encompassed.

The invention also provides methods useful for treating a TAT polypeptide-expressing cancer or alleviating one or more symptoms of the cancer in a mammal, comprising administering a therapeutically effective amount of an anti-TAT antibody, oligopeptide or organic molecule to the mammal. The antibody, oligopeptide or organic molecule therapeutic compositions can be administered short term (acute) or chronic, or intermittent as directed by physician. Also provided are methods of inhibiting the growth of, and killing a TAT polypeptide-expressing cell.

The invention also provides kits and articles of manufacture comprising at least one anti-TAT antibody, oligopeptide or organic molecule. Kits containing anti-TAT antibodies, oligopeptides or organic molecules find use, e.g., for TAT cell killing assays, for purification or immunoprecipitation of TAT polypeptide from cells. For example, for isolation and purification of TAT, the kit can contain an anti-TAT antibody, oligopeptide or organic molecule coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic molecules for detection and quantitation of TAT *in vitro*, e.g., in an ELISA or a Western blot. Such antibody, oligopeptide or organic molecule useful for detection may be provided with a label such as a fluorescent or radiolabel.

#### L. Articles of Manufacture and Kits

Another embodiment of the invention is an article of manufacture containing materials useful for the treatment of anti-TAT expressing cancer. The article of manufacture comprises a container and a label or



package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the cancer condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-TAT antibody, oligopeptide or organic molecule of the invention. The label or package insert indicates that the composition is used for treating cancer. The label or package insert will further comprise instructions for administering the antibody, oligopeptide or organic molecule composition to the cancer patient. Additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

Kits are also provided that are useful for various purposes, e.g., for TAT-expressing cell killing assays, for purification or immunoprecipitation of TAT polypeptide from cells. For isolation and purification of TAT polypeptide, the kit can contain an anti-TAT antibody, oligopeptide or organic molecule coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic molecules for detection and quantitation of TAT polypeptide *in vitro*, e.g., in an ELISA or a Western blot. As with the article of manufacture, the kit comprises a container and a label or package insert on or associated with the container. The container holds a composition comprising at least one anti-TAT antibody, oligopeptide or organic molecule of the invention. Additional containers may be included that contain, e.g., diluents and buffers, control antibodies. The label or package insert may provide a description of the composition as well as instructions for the intended *in vitro* or diagnostic use.

M. Uses for TAT Polypeptides and TAT-Polypeptide Encoding Nucleic Acids

Nucleotide sequences (or their complement) encoding TAT polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA probes. TAT-encoding nucleic acid will also be useful for the preparation of TAT polypeptides by the recombinant techniques described herein, wherein those TAT polypeptides may find use, for example, in the preparation of anti-TAT antibodies as described herein.

The full-length native sequence TAT gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length TAT cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of TAT or TAT from other species) which have a desired sequence identity to the native TAT sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence TAT. By way of example, a screening method will comprise isolating the coding region of the TAT gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety

of labels, including radionucleotides such as <sup>32</sup>P or <sup>35</sup>S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the TAT gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below. Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the TAT-encoding nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target TAT mRNA (sense) or TAT DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of TAT DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. Such methods are encompassed by the present invention. The antisense oligonucleotides thus may be used to block expression of TAT proteins, wherein those TAT proteins may play a role in the induction of cancer in mammals. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Preferred intragenic sites for antisense binding include the region incorporating the translation initiation/start codon (5'-AUG / 5'-ATG) or termination/stop codon (5'-UAA, 5'-UAG and 5'-UGA / 5'-TAA, 5'-TAG and 5'-TGA) of the open reading frame (ORF) of the gene. These regions refer to a portion of the mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation initiation or termination codon. Other preferred regions for antisense binding include: introns; exons; intron-exon junctions; the open reading frame (ORF) or "coding region," which is the region between the translation initiation codon and the translation termination codon; the 5' cap of an mRNA which comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage and includes 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap; the 5' untranslated region (5'UTR), the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA or corresponding nucleotides on the gene; and the 3' untranslated region (3'UTR), the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA or corresponding nucleotides on the gene.

Specific examples of preferred antisense compounds useful for inhibiting expression of TAT proteins include oligonucleotides containing modified backbones or non-natural internucleoside linkages. Oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotri-esters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, selenophosphates and borano-phosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most internucleotide linkage i.e. a single inverted nucleoside residue which may be abasic (the nucleobase is missing or has a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included. Representative United States patents that teach the preparation of phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos.: 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050, each of which is herein incorporated by reference.

Preferred modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH<sub>2</sub> component parts. Representative United States patents that teach the preparation of such oligonucleosides include, but are not limited to, U.S. Pat. Nos.: 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and 5,677,439, each of which is herein incorporated by reference.

In other preferred antisense oligonucleotides, both the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic

that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos.: 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al., Science, 1991, 254, 1497-1500.

Preferred antisense oligonucleotides incorporate phosphorothioate backbones and/or heteroatom backbones, and in particular  $-\text{CH}_2\text{-NH-O-CH}_2-$ ,  $-\text{CH}_2\text{-N(CH}_3\text{)-O-CH}_2-$  [known as a methylene (methylimino) or MMI backbone],  $-\text{CH}_2\text{-O-N(CH}_3\text{)-CH}_2-$ ,  $-\text{CH}_2\text{-N(CH}_3\text{)-N(CH}_3\text{)-CH}_2-$  and  $-\text{O-N(CH}_3\text{)-CH}_2\text{-CH}_2-$  [wherein the native phosphodiester backbone is represented as  $-\text{O-P-O-CH}_2-$ ] described in the above referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above referenced U.S. Pat. No. 5,602,240. Also preferred are antisense oligonucleotides having morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-alkyl, S-alkyl, or N-alkyl; O-alkenyl, S-alkenyl, or N-alkenyl; O-alkynyl, S-alkynyl or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted  $\text{C}_1$  to  $\text{C}_{10}$  alkyl or  $\text{C}_2$  to  $\text{C}_{10}$  alkenyl and alkynyl. Particularly preferred are  $\text{O}[(\text{CH}_2)_n\text{O}]_m\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{OCH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{NH}_2$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{ONH}_2$ , and  $\text{O}(\text{CH}_2)_n\text{ON}[(\text{CH}_2)_m\text{CH}_3]_2$ , where n and m are from 1 to about 10. Other preferred antisense oligonucleotides comprise one of the following at the 2' position:  $\text{C}_1$  to  $\text{C}_{10}$  lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH,  $\text{SCH}_3$ , OCN, Cl, Br, CN,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{SOCH}_3$ ,  $\text{SO}_2\text{CH}_3$ ,  $\text{ONO}_2$ ,  $\text{NO}_2$ ,  $\text{N}_3$ ,  $\text{NH}_2$ , heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy ( $2'\text{-O-CH}_2\text{CH}_2\text{OCH}_3$ , also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., Helv. Chim. Acta, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethylaminoethoxy, i.e., a  $\text{O}(\text{CH}_2)_2\text{ON}(\text{CH}_3)_2$  group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e.,  $2'\text{-O-CH}_2\text{-O-CH}_2\text{-N}(\text{CH}_3)_2$ .

A further preferred modification includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring thereby forming a bicyclic sugar moiety. The linkage is preferably a methylene ( $-\text{CH}_2-$ )<sub>n</sub> group bridging the 2' oxygen atom and the 4' carbon atom wherein n is 1 or 2. LNAs and preparation thereof are described in WO 98/39352 and WO 99/14226.

Other preferred modifications include 2'-methoxy ( $2'\text{-O-CH}_3$ ), 2'-aminopropoxy ( $2'\text{-OCH}_2\text{CH}_2\text{CH}_2$

NH<sub>2</sub>), 2'-allyl (2'-CH<sub>2</sub>-CH=CH<sub>2</sub>), 2'-O-allyl (2'-O-CH<sub>2</sub>-CH=CH<sub>2</sub>) and 2'-fluoro (2'-F). The 2'-modification may be in the arabino (up) position or ribo (down) position. A preferred 2'-arabino modification is 2'-F. Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar.

5 Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920, each of which is herein incorporated by reference in its entirety.

10 Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of  
15 adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-CH<sub>3</sub> or -CH<sub>2</sub>-C≡CH) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine  
20 and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further modified nucleobases include tricyclic pyrimidines such as phenoxazine cytidine(1H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine  
25 (2H-pyrimido[4,5-b]indol-2-one), pyridoindole cytidine (H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990, and  
30 those disclosed by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi et al, Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are preferred base substitutions, even more  
35 particularly when combined with 2'-O-methoxyethyl sugar modifications. Representative United States patents

that teach the preparation of modified nucleobases include, but are not limited to: U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos.: 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,645,985; 5,830,653; 5,763,588; 6,005,096; 5,681,941 and 5,750,692, each of which is herein incorporated by reference.

5           Another modification of antisense oligonucleotides chemically linking to the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. The compounds of the invention can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the  
10       pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugates groups include cholesterol, lipids, cation lipids, phospholipids, cationic phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve oligomer uptake, enhance oligomer resistance to degradation, and/or strengthen  
15       sequence-specific hybridization with RNA. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve oligomer uptake, distribution, metabolism or excretion. Conjugate moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety. Oligonucleotides of the invention may also be conjugated to active drug substances, for example, aspirin, warfarin, phenylbutazone,  
30       ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, flufenamic acid, folic acid, a benzothiadiazide, chlorothiazide, a diazepam, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic. Oligonucleotide-drug conjugates and their preparation are described in U.S. patent application Ser. No. 09/334,130 (filed Jun. 15, 1999) and United States patents Nos.: 4,828,979; 4,948,882; 5,218,105; 5,525,465;  
35       5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025;

4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941, each of which is herein incorporated by reference.

5 It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds which are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each  
10 made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular  
15 endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide inhibition of gene expression. Consequently, comparable results can often be obtained with shorter oligonucleotides when chimeric oligonucleotides are used, compared to phosphorothioate deoxyoligonucleotides hybridizing to the same target region. Chimeric antisense compounds of the invention may be formed as composite structures of two or more  
20 oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Preferred chimeric antisense oligonucleotides incorporate at least one 2' modified sugar (preferably 2'-O-(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>) at the 3' terminal to confer nuclease resistance and a region with at least 4 contiguous 2'-H sugars to confer RNase H activity. Such compounds have also been referred to in the art as hybrids or gapmers. Preferred gapmers have a region of 2' modified sugars (preferably 2'-O-(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>) at the 3'-terminal and  
25 at the 5' terminal separated by at least one region having at least 4 contiguous 2'-H sugars and preferably incorporate phosphorothioate backbone linkages. Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S. Pat. Nos. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, each of which is herein incorporated by reference in its entirety.

30 The antisense compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives. The compounds  
35 of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral,

rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative United States patents that teach the preparation of such uptake, distribution and/or absorption assisting formulations include, but are not limited to, U.S. Pat. Nos. 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,013,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,534,259; 5,543,152; 5,556,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO<sub>4</sub>-mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

Antisense or sense RNA or DNA molecules are generally at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710,



720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related TAT coding sequences.

5 Nucleotide sequences encoding a TAT can also be used to construct hybridization probes for mapping the gene which encodes that TAT and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

10 When the coding sequences for TAT encode a protein which binds to another protein (example, where the TAT is a receptor), the TAT can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor TAT can be used to isolate correlative ligand(s).  
15 Screening assays can be designed to find lead compounds that mimic the biological activity of a native TAT or a receptor for TAT. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

20 Nucleic acids which encode TAT or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding TAT can be used to clone genomic DNA encoding TAT in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding TAT. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S.  
25 Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for TAT transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding TAT introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding TAT. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In  
30 accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential

therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of TAT can be used to construct a TAT "knock out" animal which has a defective or altered gene encoding TAT as a result of homologous recombination between the endogenous gene encoding TAT and altered genomic DNA encoding TAT introduced into an embryonic stem cell of the animal. For example, cDNA encoding TAT can be used to clone genomic DNA encoding TAT in accordance with established techniques. A portion of the genomic DNA encoding TAT can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the TAT polypeptide.

Nucleic acid encoding the TAT polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik *et al.*, *Proc. Natl. Acad. Sci. USA* 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau

et al., Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu et al., J. Biol. Chem. 262, 4429-4432 (1987); and Wagner et al., Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson et al., Science 256, 808-813 (1992).

The nucleic acid molecules encoding the TAT polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each TAT nucleic acid molecule of the present invention can be used as a chromosome marker.

The TAT polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the TAT polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. TAT nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

This invention encompasses methods of screening compounds to identify those that mimic the TAT polypeptide (agonists) or prevent the effect of the TAT polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the TAT polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins, including e.g., inhibiting the expression of TAT polypeptide from cells. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a TAT polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the TAT polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the TAT polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the TAT polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the

immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular TAT polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1- *lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for  $\beta$ -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a TAT polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the TAT polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence

of the TAT polypeptide indicates that the compound is an antagonist to the TAT polypeptide. Alternatively, antagonists may be detected by combining the TAT polypeptide and a potential antagonist with membrane-bound TAT polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The TAT polypeptide can be labeled, such as by radioactivity, such that the number of TAT polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the TAT polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the TAT polypeptide. Transfected cells that are grown on glass slides are exposed to labeled TAT polypeptide. The TAT polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled TAT polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled TAT polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with TAT polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the TAT polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the TAT polypeptide.

Another potential TAT polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature TAT polypeptides herein, is used to design an antisense

RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the TAT polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the TAT polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the TAT polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the TAT polypeptide, thereby blocking the normal biological activity of the TAT polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Ross Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

Isolated TAT polypeptide-encoding nucleic acid can be used herein for recombinantly producing TAT polypeptide using techniques well known in the art and as described herein. In turn, the produced TAT polypeptides can be employed for generating anti-TAT antibodies using techniques well known in the art and as described herein.

Antibodies specifically binding a TAT polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders, including cancer, in the form of pharmaceutical compositions.

If the TAT polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, *e.g.*, Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

## EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

### EXAMPLE 1: Analysis of Differential TAT Polypeptide Expression by GEPIS

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and interesting EST sequences were identified by GEPIS. Gene expression profiling *in silico* (GEPIS) is a bioinformatics tool developed at Genentech, Inc. that characterizes genes of interest for new cancer therapeutic targets. GEPIS takes advantage of large amounts of EST sequence and library information to determine gene expression profiles. GEPIS is capable of determining the expression profile of a gene based upon its proportional correlation with the number of its occurrences in EST databases, and it works by integrating the LIFESEQ® EST relational database and Genentech proprietary information in a stringent and statistically meaningful way. In this example, GEPIS is used to identify and cross-validate novel tumor antigens, although GEPIS can be configured to perform either very specific analyses or broad screening tasks. For the initial screen, GEPIS is used to identify EST sequences from the LIFESEQ® database that correlate

to expression in a particular tissue or tissues of interest (often a tumor tissue of interest). Then, GEPIS was employed to generate a complete tissue expression profile for the various sequences of interest. Using this type of screening bioinformatics, various TAT polypeptides (and their encoding nucleic acid molecules) were identified as being significantly overexpressed in a particular type of cancer or certain cancers as compared to other cancers and/or normal non-cancerous tissues. The rating of GEPIS hits is based upon several criteria including, for example, tissue specificity, tumor specificity and expression level in normal essential and/or normal proliferating tissues. The following is a list of molecules whose tissue expression profile as determined by GEPIS evidences significant upregulation of expression in a specific tumor or tumors as compared to other tumor(s) and/or normal tissues and optionally relatively low expression in normal essential and/or normal proliferating tissues.

Under each tissue heading shown below is a list of the cDNA sequences that are detectably overexpressed in tumor tissue of the indicated tissue type as compared to normal non-tumor tissue of the same tissue type. As such, the molecules listed below (and the polypeptides they encode) are excellent nucleic acid (and polypeptide) targets for the diagnosis and therapy of cancer in mammals.

#### PERIPHERAL NERVOUS SYSTEM

DNA324303	DNA324573	DNA324681	DNA325296	DNA325405	DNA325407
DNA325408	DNA325409	DNA325410	DNA325449	DNA325503	DNA326083
DNA326231	DNA188229	DNA327080	DNA327081	DNA327082	

#### BRAIN

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ADIPOSE

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WHOLE BLOOD

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PITUITARY GLAND

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SKIN

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ENDOCRINE

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STOMACH

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BONE

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**EXAMPLE 2: Use of TAT as a hybridization probe**

15 The following method describes use of a nucleotide sequence encoding TAT as a hybridization probe for, i.e., diagnosis of the presence of a tumor in a mammal.

DNA comprising the coding sequence of full-length or mature TAT as disclosed herein can also be employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of TAT) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled TAT-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

5 DNAs having a desired sequence identity with the DNA encoding full-length native sequence TAT can then be identified using standard techniques known in the art.

### EXAMPLE 3: Expression of TAT in *E. coli*

10 This example illustrates preparation of an unglycosylated form of TAT by recombinant expression in *E. coli*.

The DNA sequence encoding TAT is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR  
15 amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the TAT coding region, lambda transcriptional terminator, and an argU gene.

20 The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

25 Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized TAT protein can then be purified using a metal chelating column under conditions that allow tight binding of  
30 the protein.

TAT may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding TAT is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation  
35 column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110

5 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.71 g sodium citrate•2H<sub>2</sub>O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO<sub>4</sub>) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

10 *E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

20 The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

30 Fractions containing the desired folded TAT polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using

this technique(s).

EXAMPLE 4: Expression of TAT in mammalian cells

This example illustrates preparation of a potentially glycosylated form of TAT by recombinant expression in mammalian cells.

5       The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the TAT DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the TAT DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called pRK5-TAT.

10       In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-TAT DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl<sub>2</sub>. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO<sub>4</sub>, and a precipitate is allowed to form for 10 minutes at 25°C. The  
15       precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

      Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml <sup>35</sup>S-cysteine and 200 µCi/ml <sup>35</sup>S-methionine.  
20       After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of TAT polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

      In an alternative technique, TAT may be introduced into 293 cells transiently using the dextran sulfate  
25       method described by Sompayrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-TAT DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 µg/ml bovine insulin and  
30       0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed TAT can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

      In another embodiment, TAT can be expressed in CHO cells. The pRK5-TAT can be transfected into  
CHO cells using known reagents such as CaPO<sub>4</sub> or DEAE-dextran. As described above, the cell cultures can  
35       be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as <sup>35</sup>S-methionine. After determining the presence of TAT polypeptide, the culture medium may be replaced

with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed TAT can then be concentrated and purified by any selected method.

Epitope-tagged TAT may also be expressed in host CHO cells. The TAT may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged TAT insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged TAT can then be concentrated and purified by any selected method, such as by  $\text{Ni}^{2+}$ -chelate affinity chromatography.

TAT may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect<sup>®</sup> (Quiagen), Dosper<sup>®</sup> or Fugene<sup>®</sup> (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately  $3 \times 10^7$  cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2  $\mu\text{m}$  filtered PS20 with 5% 0.2  $\mu\text{m}$  diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with  $3 \times 10^5$  cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at  $1.2 \times 10^6$  cells/mL. On day 0, the cell number pH is determined. On day

1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 µm filter. The filtrate was  
5 either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional  
10 equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer  
15 before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 µL of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

20 Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

#### EXAMPLE 5: Expression of TAT in Yeast

The following method describes recombinant expression of TAT in yeast.

25 First, yeast expression vectors are constructed for intracellular production or secretion of TAT from the ADH2/GAPDH promoter. DNA encoding TAT and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of TAT. For secretion, DNA encoding TAT can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native TAT signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory  
30 signal/leader sequence, and linker sequences (if needed) for expression of TAT.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

35 Recombinant TAT can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The



concentrate containing TAT may further be purified using selected column chromatography resins.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

**EXAMPLE 6: Expression of TAT in Baculovirus-Infected Insect Cells**

5 The following method describes recombinant expression of TAT in Baculovirus-infected insect cells.

The sequence coding for TAT is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding TAT or the desired portion of the coding sequence of  
10 TAT such as the sequence encoding an extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus  
15 DNA (Pharmlngen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged TAT can then be purified, for example, by Ni<sup>2+</sup>-chelate affinity  
20 chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl<sub>2</sub>; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm  
25 filter. A Ni<sup>2+</sup>-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A<sub>280</sub> with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching  
30 A<sub>280</sub> baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni<sup>2+</sup>-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His<sub>6</sub>-tagged TAT are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) TAT can be performed using known  
35 chromatography techniques, including for instance, Protein A or protein G column chromatography.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using

this technique(s).

**EXAMPLE 7: Preparation of Antibodies that Bind TAT**

This example illustrates preparation of monoclonal antibodies which can specifically bind TAT.

5 Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified TAT, fusion proteins containing TAT, and cells expressing recombinant TAT on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

10 Mice, such as Balb/c, are immunized with the TAT immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice  
15 by retro-orbital bleeding for testing in ELISA assays to detect anti-TAT antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of TAT. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells  
20 which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against TAT. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against TAT is within the skill in the art.

25 The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-TAT monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

30 **EXAMPLE 8: Purification of TAT Polypeptides Using Specific Antibodies**

Native or recombinant TAT polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-TAT polypeptide, mature TAT polypeptide, or pre-TAT polypeptide is purified by immunoaffinity chromatography using antibodies specific for the TAT polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-TAT  
35 polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium

sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of TAT polypeptide by preparing a fraction from cells containing TAT polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble TAT polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble TAT polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of TAT polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/TAT polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and TAT polypeptide is collected.

#### EXAMPLE 9: *In Vitro* Tumor Cell Killing Assay

Mammalian cells expressing the TAT polypeptide of interest may be obtained using standard expression vector and cloning techniques. Alternatively, many tumor cell lines expressing TAT polypeptides of interest are publicly available, for example, through the ATCC and can be routinely identified using standard ELISA or FACS analysis. Anti-TAT polypeptide monoclonal antibodies (and toxin conjugated derivatives thereof) may then be employed in assays to determine the ability of the antibody to kill TAT polypeptide expressing cells *in vitro*.

For example, cells expressing the TAT polypeptide of interest are obtained as described above and plated into 96 well dishes. In one analysis, the antibody/toxin conjugate (or naked antibody) is included throughout the cell incubation for a period of 4 days. In a second independent analysis, the cells are incubated for 1 hour with the antibody/toxin conjugate (or naked antibody) and then washed and incubated in the absence of antibody/toxin conjugate for a period of 4 days. Cell viability is then measured using the CellTiter-Glo Luminescent Cell Viability Assay from Promega (Cat# G7571). Untreated cells serve as a negative control.

#### EXAMPLE 10: *In Vivo* Tumor Cell Killing Assay

To test the efficacy of conjugated or unconjugated anti-TAT polypeptide monoclonal antibodies, anti-TAT antibody is injected intraperitoneally into nude mice 24 hours prior to receiving tumor promoting cells subcutaneously in the flank. Antibody injections continue twice per week for the remainder of the study. Tumor volume is then measured twice per week.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to

5 practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. Isolated nucleic acid having a nucleotide sequence that has at least 80 % nucleic acid sequence identity to:
  - (a) a DNA molecule encoding the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
  - 5 (b) a DNA molecule encoding the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
  - (c) a DNA molecule encoding an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
  - (d) a DNA molecule encoding an extracellular domain of the polypeptide shown in any one of Figures 10 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
  - (e) the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
  - (f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
  - (g) the complement of (a), (b), (c), (d), (e) or (f).
- 15 2. Isolated nucleic acid having:
  - (a) a nucleotide sequence that encodes the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
  - (b) a nucleotide sequence that encodes the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
  - 20 (c) a nucleotide sequence that encodes an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
  - (d) a nucleotide sequence that encodes an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
  - (e) the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
  - 25 (f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
  - (g) the complement of (a), (b), (c), (d), (e) or (f).
3. Isolated nucleic acid that hybridizes to:
  - (a) a nucleic acid that encodes the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
  - 30 (b) a nucleic acid that encodes the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
  - (c) a nucleic acid that encodes an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
  - 35 (d) a nucleic acid that encodes an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

- (e) the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (g) the complement of (a), (b), (c), (d), (e) or (f).
4. The nucleic acid of Claim 3, wherein the hybridization occurs under stringent conditions.
5. The nucleic acid of Claim 3 which is at least about 5 nucleotides in length.
6. An expression vector comprising the nucleic acid of Claim 1, 2 or 3.
7. The expression vector of Claim 6, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector.
8. A host cell comprising the expression vector of Claim 7.
9. The host cell of Claim 8 which is a CHO cell, an *E. coli* cell or a yeast cell.
10. A process for producing a polypeptide comprising culturing the host cell of Claim 8 under conditions suitable for expression of said polypeptide and recovering said polypeptide from the cell culture.
11. An isolated polypeptide having at least 80% amino acid sequence identity to:
- (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).
12. An isolated polypeptide having:
- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

13. A chimeric polypeptide comprising the polypeptide of Claim 11 or 12 fused to a heterologous polypeptide.
14. The chimeric polypeptide of Claim 13, wherein said heterologous polypeptide is an epitope tag sequence or an Fc region of an immunoglobulin.
15. An isolated antibody that binds to a polypeptide having at least 80% amino acid sequence identity to:
- 5
- (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
  - (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
  - (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
  - 10 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
  - (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
  - 15 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).
16. An isolated antibody that binds to a polypeptide having:
- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
  - (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
  - 20 (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
  - (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
  - 25 (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
  - (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).
17. The antibody of Claim 15 or 16 which is a monoclonal antibody.
- 30 18. The antibody of Claim 15 or 16 which is an antibody fragment.
19. The antibody of Claim 15 or 16 which is a chimeric or a humanized antibody.
20. The antibody of Claim 15 or 16 which is conjugated to a growth inhibitory agent.
21. The antibody of Claim 15 or 16 which is conjugated to a cytotoxic agent.
22. The antibody of Claim 21, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
- 35 23. The antibody of Claim 21, wherein the cytotoxic agent is a toxin.

24. The antibody of Claim 23, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
25. The antibody of Claim 23, wherein the toxin is a maytansinoid.
26. The antibody of Claim 15 or 16 which is produced in bacteria.
27. The antibody of Claim 15 or 16 which is produced in CHO cells.
- 5 28. The antibody of Claim 15 or 16 which induces death of a cell to which it binds.
29. The antibody of Claim 15 or 16 which is detectably labeled.
30. An isolated nucleic acid having a nucleotide sequence that encodes the antibody of Claim 15 or 16.
31. An expression vector comprising the nucleic acid of Claim 30 operably linked to control sequences recognized by a host cell transformed with the vector.
- 10 32. A host cell comprising the expression vector of Claim 31.
33. The host cell of Claim 32 which is a CHO cell, an *E. coli* cell or a yeast cell.
34. A process for producing an antibody comprising culturing the host cell of Claim 32 under conditions suitable for expression of said antibody and recovering said antibody from the cell culture.
- 15 35. An isolated oligopeptide that binds to a polypeptide having at least 80% amino acid sequence identity to:
- (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- 20 (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- 25 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).
36. An isolated oligopeptide that binds to a polypeptide having:
- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- 30 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- 35 (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355



(SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

37. The oligopeptide of Claim 35 or 36 which is conjugated to a growth inhibitory agent.

38. The oligopeptide of Claim 35 or 36 which is conjugated to a cytotoxic agent.

5 39. The oligopeptide of Claim 38, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

40. The oligopeptide of Claim 38, wherein the cytotoxic agent is a toxin.

41. The oligopeptide of Claim 40, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

10 42. The oligopeptide of Claim 40, wherein the toxin is a maytansinoid.

43. The oligopeptide of Claim 35 or 36 which induces death of a cell to which it binds.

44. The oligopeptide of Claim 35 or 36 which is detectably labeled.

45. A TAT binding organic molecule that binds to a polypeptide having at least 80% amino acid sequence identity to:

15 (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

20 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

25 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

46. The organic molecule of Claim 45 that binds to a polypeptide having:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

30 (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

35 (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown

in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

47. The organic molecule of Claim 45 or 46 which is conjugated to a growth inhibitory agent.
48. The organic molecule of Claim 45 or 46 which is conjugated to a cytotoxic agent.
49. The organic molecule of Claim 48, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
- 5 50. The organic molecule of Claim 48, wherein the cytotoxic agent is a toxin.
51. The organic molecule of Claim 50, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
52. The organic molecule of Claim 50, wherein the toxin is a maytansinoid.
53. The organic molecule of Claim 45 or 46 which induces death of a cell to which it binds.
- 10 54. The organic molecule of Claim 45 or 46 which is detectably labeled.
55. A composition of matter comprising:
- (a) the polypeptide of Claim 11;
- (b) the polypeptide of Claim 12;
- (c) the chimeric polypeptide of Claim 13;
- 15 (d) the antibody of Claim 15;
- (e) the antibody of Claim 16;
- (f) the oligopeptide of Claim 35;
- (g) the oligopeptide of Claim 36;
- (h) the TAT binding organic molecule of Claim 45; or
- 20 (i) the TAT binding organic molecule of Claim 46; in combination with a carrier.
56. The composition of matter of Claim 55, wherein said carrier is a pharmaceutically acceptable carrier.
57. An article of manufacture comprising:
- (a) a container; and
- 25 (b) the composition of matter of Claim 55 contained within said container.
58. The article of manufacture of Claim 57 further comprising a label affixed to said container, or a package insert included with said container, referring to the use of said composition of matter for the therapeutic treatment of or the diagnostic detection of a cancer.
59. A method of inhibiting the growth of a cell that expresses a protein having at least 80% amino acid sequence identity to:
- 30 (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
- 35 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-

6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising contacting said cell with an antibody, oligopeptide or organic molecule that binds to said protein, the binding of said antibody, oligopeptide or organic molecule to said protein thereby causing an inhibition of growth of said cell.

60. The method of Claim 59; wherein said antibody is a monoclonal antibody.

61. The method of Claim 59, wherein said antibody is an antibody fragment.

62. The method of Claim 59, wherein said antibody is a chimeric or a humanized antibody.

63. The method of Claim 59, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

64. The method of Claim 59, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

65. The method of Claim 64, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

66. The method of Claim 64, wherein the cytotoxic agent is a toxin.

67. The method of Claim 66, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

68. The method of Claim 66, wherein the toxin is a maytansinoid.

69. The method of Claim 59, wherein said antibody is produced in bacteria.

70. The method of Claim 59, wherein said antibody is produced in CHO cells.

71. The method of Claim 59, wherein said cell is a cancer cell.

72. The method of Claim 71, wherein said cancer cell is further exposed to radiation treatment or a chemotherapeutic agent.

73. The method of Claim 71, wherein said cancer cell is selected from the group consisting of a breast cancer cell, a colorectal cancer cell, a lung cancer cell, an ovarian cancer cell, a central nervous system cancer cell, a liver cancer cell, a bladder cancer cell, a pancreatic cancer cell, a cervical cancer cell, a melanoma cell and a leukemia cell.

74. The method of Claim 71, wherein said protein is more abundantly expressed by said cancer cell as compared to a normal cell of the same tissue origin.

75. The method of Claim 59 which causes the death of said cell.

76. The method of Claim 59, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures

1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

5 (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

77. A method of therapeutically treating a mammal having a cancerous tumor comprising cells that express a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

10 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

15 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

20 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising administering to said mammal a therapeutically effective amount of an antibody, oligopeptide or organic molecule that binds to said protein, thereby effectively treating said mammal.

78. The method of Claim 77, wherein said antibody is a monoclonal antibody.

79. The method of Claim 77, wherein said antibody is an antibody fragment.

80. The method of Claim 77, wherein said antibody is a chimeric or a humanized antibody.

25 81. The method of Claim 77, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

82. The method of Claim 77, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

30 83. The method of Claim 82, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

84. The method of Claim 82, wherein the cytotoxic agent is a toxin.

85. The method of Claim 84, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

86. The method of Claim 84, wherein the toxin is a maytansinoid.

35 87. The method of Claim 77, wherein said antibody is produced in bacteria.

88. The method of Claim 77, wherein said antibody is produced in CHO cells.

89. The method of Claim 77, wherein said tumor is further exposed to radiation treatment or a chemotherapeutic agent.

90. The method of Claim 77, wherein said tumor is a breast tumor, a colorectal tumor, a lung tumor, an ovarian tumor, a central nervous system tumor, a liver tumor, a bladder tumor, a pancreatic tumor, or a cervical tumor.

5 91. The method of Claim 77, wherein said protein is more abundantly expressed by the cancerous cells of said tumor as compared to a normal cell of the same tissue origin.

92. The method of Claim 77, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

10 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

15 (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

20 93. A method of determining the presence of a protein in a sample suspected of containing said protein, wherein said protein has at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

25 (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

30 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising exposing said sample to an antibody, oligopeptide or organic molecule that binds to said protein and determining binding of said antibody, oligopeptide or organic molecule to said protein in said sample, wherein binding of the antibody, oligopeptide or organic molecule to said protein is indicative of the presence of said protein in said sample.

35 94. The method of Claim 93, wherein said sample comprises a cell suspected of expressing said protein.

95. The method of Claim 94, wherein said cell is a cancer cell.

96. The method of Claim 93, wherein said antibody, oligopeptide or organic molecule is detectably labeled.

97. The method of Claim 93, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

5 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

10 (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

15 98. A method of diagnosing the presence of a tumor in a mammal, said method comprising determining the level of expression of a gene encoding a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

20 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

25 (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

30 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), in a test sample of tissue cells obtained from said mammal and in a control sample of known normal cells of the same tissue origin, wherein a higher level of expression of said protein in the test sample, as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test sample was obtained.

99. The method of Claim 98, wherein the step of determining the level of expression of a gene encoding said protein comprises employing an oligonucleotide in an *in situ* hybridization or RT-PCR analysis.

100. The method of Claim 98, wherein the step determining the level of expression of a gene encoding said protein comprises employing an antibody in an immunohistochemistry or Western blot analysis.

101. The method of Claim 98, wherein said protein has:

- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
- 5 (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown
- 10 in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

102. A method of diagnosing the presence of a tumor in a mammal, said method comprising contacting a test sample of tissue cells obtained from said mammal with an antibody, oligopeptide or organic molecule that binds to a protein having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- 15 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- 20 (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), and detecting the formation of a complex between said antibody,
- 25 oligopeptide or organic molecule and said protein in the test sample, wherein the formation of a complex is indicative of the presence of a tumor in said mammal.

103. The method of Claim 102, wherein said antibody, oligopeptide or organic molecule is detectably labeled.

104. The method of Claim 102, wherein said test sample of tissue cells is obtained from an

30 individual suspected of having a cancerous tumor.

105. The method of Claim 102, wherein said protein has:

- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- 35 (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

5 (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

106. A method for treating or preventing a cell proliferative disorder associated with increased expression or activity of a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

10 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

15 (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

20 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising administering to a subject in need of such treatment an effective amount of an antagonist of said protein, thereby effectively treating or preventing said cell proliferative disorder.

107. The method of Claim 106, wherein said cell proliferative disorder is cancer.

108. The method of Claim 106, wherein said antagonist is an anti-TAT polypeptide antibody, TAT binding oligopeptide, TAT binding organic molecule or antisense oligonucleotide.

25 109. A method of binding an antibody, oligopeptide or organic molecule to a cell that expresses a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

30 (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

35 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising contacting said cell with an antibody,



oligopeptide or organic molecule that binds to said protein and allowing the binding of the antibody, oligopeptide or organic molecule to said protein to occur, thereby binding said antibody, oligopeptide or organic molecule to said cell.

110. The method of Claim 109, wherein said antibody is a monoclonal antibody.
111. The method of Claim 109, wherein said antibody is an antibody fragment.
- 5 112. The method of Claim 109, wherein said antibody is a chimeric or a humanized antibody.
113. The method of Claim 109, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.
114. The method of Claim 109, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.
- 10 115. The method of Claim 114, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
116. The method of Claim 114, wherein the cytotoxic agent is a toxin.
117. The method of Claim 116, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
- 15 118. The method of Claim 116, wherein the toxin is a maytansinoid.
119. The method of Claim 109, wherein said antibody is produced in bacteria.
120. The method of Claim 109, wherein said antibody is produced in CHO cells.
121. The method of Claim 109, wherein said cell is a cancer cell.
122. The method of Claim 121, wherein said cancer cell is further exposed to radiation treatment or a chemotherapeutic agent.
- 20 123. The method of Claim 121, wherein said cancer cell is selected from the group consisting of a breast cancer cell, a colorectal cancer cell, a lung cancer cell, an ovarian cancer cell, a central nervous system cancer cell, a liver cancer cell, a bladder cancer cell, a pancreatic cancer cell, a cervical cancer cell, a melanoma cell and a leukemia cell.
- 25 124. The method of Claim 123, wherein said protein is more abundantly expressed by said cancer cell as compared to a normal cell of the same tissue origin.
125. The method of Claim 109 which causes the death of said cell.
126. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
- 30 127. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for treating a tumor.
128. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.
129. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
- 35 130. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of

medicament for treating a tumor.

131. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

132. Use of a host cell as claimed in any of Claims 8, 9, 32, or 33 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

5 133. Use of a host cell as claimed in any of Claims 8, 9, 32 or 33 in the preparation of a medicament for treating a tumor.

134. Use of a host cell as claimed in any of Claims 8, 9, 32 or 33 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

135. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

136. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for treating a tumor.

5 137. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

138. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

139. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for treating a tumor.

10 140. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

141. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

15 142. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for treating a tumor.

143. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

144. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

20 145. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for treating a tumor.

146. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

25 147. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

148. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for treating a tumor.

149. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

30 150. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

151. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for treating a tumor.

152. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

153. A method for inhibiting the growth of a cell, wherein the growth of said cell is at least in part dependent upon a growth potentiating effect of a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

5 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

10 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

15 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising contacting said protein with an antibody, oligopeptide or organic molecule that binds to said protein, thereby inhibiting the growth of said cell.

154. The method of Claim 153, wherein said cell is a cancer cell.

155. The method of Claim 153, wherein said protein is expressed by said cell.

156. The method of Claim 153, wherein the binding of said antibody, oligopeptide or organic molecule to said protein antagonizes a cell growth-potentiating activity of said protein.

20 157. The method of Claim 153, wherein the binding of said antibody, oligopeptide or organic molecule to said protein induces the death of said cell.

158. The method of Claim 153, wherein said antibody is a monoclonal antibody.

159. The method of Claim 153, wherein said antibody is an antibody fragment.

160. The method of Claim 153, wherein said antibody is a chimeric or a humanized antibody.

25 161. The method of Claim 153, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

162. The method of Claim 153, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

30 163. The method of Claim 162, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

164. The method of Claim 162, wherein the cytotoxic agent is a toxin.

165. The method of Claim 164, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

166. The method of Claim 164, wherein the toxin is a maytansinoid.

35 167. The method of Claim 153, wherein said antibody is produced in bacteria.

168. The method of Claim 153, wherein said antibody is produced in CHO cells.

169. The method of Claim 153, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

5 (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

10 (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

170. A method of therapeutically treating a tumor in a mammal, wherein the growth of said tumor is at least in part dependent upon a growth potentiating effect of a protein having at least 80% amino acid sequence identity to:

15 (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

20 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

25 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising contacting said protein with an antibody, oligopeptide or organic molecule that binds to said protein, thereby effectively treating said tumor.

171. The method of Claim 170, wherein said protein is expressed by cells of said tumor.

172. The method of Claim 170, wherein the binding of said antibody, oligopeptide or organic molecule to said protein antagonizes a cell growth-potentiating activity of said protein.

30 173. The method of Claim 170, wherein said antibody is a monoclonal antibody.

174. The method of Claim 170, wherein said antibody is an antibody fragment.

175. The method of Claim 170, wherein said antibody is a chimeric or a humanized antibody.

176. The method of Claim 170, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

35 177. The method of Claim 170, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

178. The method of Claim 177, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

179. The method of Claim 177, wherein the cytotoxic agent is a toxin.

180. The method of Claim 179, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

5 181. The method of Claim 179, wherein the toxin is a maytansinoid.

182. The method of Claim 170, wherein said antibody is produced in bacteria.

183. The method of Claim 170, wherein said antibody is produced in CHO cells.

184. The method of Claim 170, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

10 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

15 (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

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**FIGURE 1**

ATCACATGCCTATCATATAGTAAAAACCCAGCCCATGGCCCCTAACAGGGGCCCTCTCAGCCCTCCTAATGACCTC  
CGGCCTAGCCATGTGATTTCACTTCCACTCCACAACCCTCCTCATACTAGGCCTACTAACCAACACACTAACCAT  
ATACCAATGATGGCGCGATGTAACACGAGAAAGCACATACCAAGGCCACCACACACCACCTGTCCAGAAAGGCCT  
TCGATACGGGATAATCCTATTTATTACCTCAGAAGTTTTTTTCTCGCAGGATTTTTCTGAGCCTTTTACCACTC  
CAGCCTAGCTCCCACCCCCCACTAGGGGGACACTGGCCCCCAACAGGCATCACCCCGCTAAATCCCCTAGAAGT  
CCCACTCCTAAACACATCCGTATTACTCGCATCAGGGGTATCAATCACCTGAGCTCACCATAGTCTAATAGTCTA  
TTTTACCCTCCTACAAGCCTCAGAGTACTTCGAG

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**FIGURE 2**

TCTAATACCTATTGATCTGTCACTTTCTCCCATCACGCTCAGGTGGGACCATTTCAGTTGCAGGAAAACAAGCTTA  
ACACGCCCCTAATTCTACATTATGGTGAGTTCTATAATTATTTTATTATATATTACAGTGTAAATGGAAATA  
AAGTGCCTAATAAATGCAAATGTGCTTACATCTTTTGGCCCAGCTCCTACCTCCCGGCAGCCTCTCCAGGCCCAG  
AACTTTCTCCAGTCAGCCTCTACAGACCAAGCTCATGACTCACAATGGCCTATTTAGGCCCATACCCTATGTCAC  
GGCAGCCTCCGCAGATGAGGCTACTGCCTCACAACAGCCTCCACAGGCACAGCTCCATCGTTACAATGGCCTCTT  
TAGACCCAGCTCCTGCCTCCAGCCTTCTCTCCAGGCCCTGAACCTTTCTCAAGTCGACCTCACCAGGCCAGCTC  
ATGCTTCTTTGCAGCCTCTCCAGGCCAGCTCCTGCATCTTGGTGGCCCTCCAGGCCAGCCTCTGCCTCCCGT  
CAGCCTCTACAGTCCCAAAGTCTGCCTCACAGCAGATTCTTCAGCCCAGCATCTACCTCACTTGGACCCTCCAG  
ACCCAGATGGTGTCTCACTGTGGCATCCTCAGGCGAAGCTCCTGCCTTTTCGGCAGCCTCTCCAGGCCAGCTCCT  
CCTGCCTCCAGTGGCCTCTTTTCGGCCCAGCCCAGCTCATGCCTCCCGGCGGCCTTCCCAAGCCCCGCTTTTGAC  
TTTCGGTGGCCTCTGCAGGCCTCGACAAGGCCAGCCTCCTGCCTCCCGAAGGCCTGCACAGGCCAGCCTCTGC  
CTCACAGCGGACTCTC



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**FIGURE 3**

CAAGCTCATGACTCACAAATGGCCTATTTAGGCCCATACCCTACGTCACGGCAGCCTCCGCAGATGAGCCTACTGC  
CTCACAAACAGCCTCCACAGGCACAGCTCCATCGTTACAATGGCCTCTTTAGACCCAGCTCCTGCCTCCCAGCCTT  
CTCTCCAGGCTCTGAACTTTCTCAGGTCTCCCTCTGTTGTCCAAGGCTGGAGTGTAGTAGTGCTATCGCAGCTGA  
CTGCAGCCTCAACCTTCCAGGCTGAAGCGATCCTCCCACCTCAACCTCCCACGTGGCTGAGACTACAGGTGCTTG  
CCACTATGCCCAACTAACATTTGGAATTTTCGTATACGTGGATTCCAGAGGGGTGACAGCGAAACGTGGGACCAT  
TCAGTTGCAGGAAAACAAGCTTAACACGCCCACTAATTCTACATTATGCTCCTACCTCCCGGCAGCCTCTCCAGG  
CCCAGAACTTTCTCCAGTCAGCCTCTACAGACCAAGCTCATGACTCACAAATG

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**FIGURE 4**

CGTCGGCCCCGGCCCCCAGCAGCCTCCAAAGCCCTGTGACTCACAGCCCTGCTTCCACGGGGGGACCTGCCAG  
GACTGGGCATTGGGCGGGGGCTTCACTGTCAGCTGCCCCGAGGAGGGGAGGGCGCCGTCTGTGAGAAGGTGCTT  
GGCGCCCCGTGCGGGCCCTTCGAGGGCCGCTCCTTCCCTGGCCCTCCCCACTCTCCGCGCCTACCACACGCTGCGC  
CTGGCACTGGAATTCGGGGCGCTGGAGCCTCAGGGGCTGCTGCTGTACAATGGCAACGCCCCGGGGCAAGGACTTC  
CTGGCATTGGCGCTGCTAGATGGCCGCGTGCAGCTCAGGTTTGACACAGGTTTCGGGGCCGGCGGTGCTGACCAGT  
GCCGTGCCGGTAGAGCCGGGCCAGTGGCACCAGCTGGAGCTGTCCCGGCACTGGCGCCGGGGACCCCTCTCGGTG  
GATGGTGAGACCCCTGTTCTGGGCGAGAGTCCCACTGGCACCAGCGGCTCAACCTGGACACAGACCTCTTTGTG  
GGCGGCGTACCCGAGGACCAGGCTGCCGTGGCGCTGGAGCGGACCTTCGTGGGCGCCGGCCTGAGGGGGTGATC  
CGTTTGCTGGACGTCAACAACCAGCGCCTGGAGCTTGGCATTGGGCGGGGGCTGCCACCCGAGGCTCTGGCGTG  
GGCAAGTGCGGGGACCACCCCTGCCTGCCCAACCCCTGCCATGGCGGGGGCCCATGCCAGAACCTGGAGGCTGGA  
AGGTTCCATTGCCAGTGCCCGCCCGCGCGCTCGGACCAACCTGTGCCGATGAGAAGAGCCCTGCCAGCCCAAC  
CCCTGCCATGGGGCGCGCCCTGCCGTGTGCTGCCGAGGGTGGTGCTCAGTGCGAGTGCCCCCTGGGGCGTGAG  
GGCACCTTCTGCCAGACAGCCTCGGGGCAGGACGGCTCTGGGCCCTTCTGGCTGACTTCAACGGCTTCTCCAC  
CTGGAGCTGAGAGGCTGCACACCTTTGCACGGGACCTGGGGGAGAAGATGGCGCTGGAGGTCGTGTTCTGGCA  
CGAGGCCCCAGCGGCTCTGCTCTACAACGGGCAGAAGACGGACGGCAAGGGGACTTCGTGTGCTGGCACTG  
CGGGACCGCGCCTGGAGTTCCGCTACGACCTGGGCAAGGGGGCAGCGGTCAATCAGGAGCAGGAGCCAGTCACC  
CTGGGAGCCTGGACAGGGTCTCACTGGAGCGAAACGGCCGAAGGTGCCCTGCGTGTGGGCGACGGCCCCCGT  
GTGTTGGGGGAGTCCCCGGTTCCGCACACCGTCTCTCAACCTGAAGGAGCCGCTCTACGTAGGGGGCGCTCCCGAC  
TTCAGCAAGCTGGCCCGTGTGCTGCTGCCGTGCTCTGGCTTCGACGGTGCCATCCAGCTGGTCTCCCTCGGAGGC  
CGCCAGCTGCTGACCCCGGAGCAGTGTGCGGCAGGTGGACGTACGTCTCTTGCAGGTACCCCTGCACCCGG  
GCCTCAGGCCACCCCTGCCTCAATGGGGCCTCTGCTGCCGAGGGAGGCTGCCTATGTGTGCTGTGTCCCGG  
GGATTCTCAGGACCGCACTGCGAGAAGGGGCTGGTGGAGAAGTCAGCGGGGACGTGGATACTTGGCCTTTGAC  
GGGCGGACCTTTGTGAGTACCTCAACGCTGTGACCGAGAGCGAGAAGGCACTGCAGAGCAACCACTTTGAAGT  
AGCCTGCGCACTGAGGACAGCAGGGGCTGGTGTCTGGAGTGGCAAGGCCACGGAGCGGGCAGACTATGTGGCA  
CTGGCCATTGTGGACGGGCACCTGCAACTGAGCTACAACCTGGGCTCCAGCCCGTGGTGTGCGTTCCACCGTG  
CCCGTCAACACCAACCGCTGGTTGCGGGTCTGGGACATAGGGAGCAGAGGAAGGTTCCCTGCAGGTGGGCAAT  
GAGGCCCCCTGTGACCGGCTCCTCCCCGTGGGCGCCAGCAGCTGGACACTGATGGAGCCCTGTGGCTTGGGGG  
CTGCCGAGCTGCCCGTGGGCCAGCACTGCCAAGGCTACGGCACAGGCTTTGTGGGCTGCTTGGGGACGTG  
GTGGTGGGCGGCGACCCGCTGCACCTGCTGGAGGACGCGCTACCAAGCCAGAGCTGCGGCCCTGCCCAACCCCA  
TGAGCTGGCACCAGAGCCCCGCGCCGCTGTAATTATTTTCTATTTTGTAAACTTGTGCTTTTGTATATGATT  
TTCTTGCTGAGTGTGGCCGGAGGACTGCTGGCCCGGCTCCCTTCCGTCCAGGCAGCGTGTGCTGACGACAGA  
CCTAGTGCCGAGGGATGGACAGGCGAGGTGGCAGCGTGGAGGGCTCGGCGTGGATGGCAGCCTCAGGACACAC  
CCCTGCCTCAAGGTGCTGAGCCCCCGCTTGCAGCTGCGCCTGCCCCACGGTGTCCCGCGGGAAGCAGCCCCGG  
CTCCTGAATACCCCTCGCTCCGTGAGCGGGACTCGTGTCCAGAGAGGAAGGGGCTGCTGAGGCTGTATGGGGC  
CCTTCTCCGGGTGACCCACAGGGCCTTTTCAAGCCCCATTGAGCTGCTCCTTCTGTGTGTGCTCTGGGCC  
CTGCCTCGGCCTCTGCGCCAATACTGTGACTTCCAAACAATGTTACTGCTGGGCACAGCTCTGCGTGTGCTCCCG  
TGCTGCTGCGCCAGCCCCAGGCTGCTGAGGAGCAGAGGCCAGACCAGGGCCGATCTGGGTGTCTGACCTCAG  
CTGGCCCTGCCAGCCACCCTGGACATGACCGTATCCCTCTGCCACACCCAGGCCCTGCGAGGGGTATCGAGA  
GGAGCTCACTGTGGGATGGGGTTGACCTCTGCCGCTGCTGGGTATCTGGGCTGGCCATGGCTGTGTCTTCA  
TGTGTTGATTTTATTTGACCCCTGGAGTGGTGGTCTCATCTTTCCCATCTCGCCTGAGAGCGGCTGAGGGCTGC  
CTCACTGCAAACTCTCCACAGCGTCAGTGAAAGTCGTCTTGTCTCAGAATGACCAGGGGCCAGCCAGTGCT  
GACCAAGGTCAAGGGGAGGTGAGAGGTGGCAGGGATGGCTCCGAAGCCAGAAATGCCTTAACTGCAACGTCC  
CGTCCCTTCCCCACCCCATCCCATCCCCACCCCAAGCCCCAGCCCCAGTCTCTAGGAGCAGGACCCGATGAAG  
CGGGCGGCGGTGGGGCTGGGTGCCGTGTTACTAACTCTAGTATGTTTCTGTGTCAATCGCTGTGAAATAAAGTCT  
GAAAACCTT

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**FIGURE 5**

MLNSSLMRITLRNLEEVEFCVEDKPGTHFTVPPTPPDACRGMLCGFGAVCEPNAEGPGRASCVCKKSPCPSVVA  
PVCGSDASTYSNECELQRAQCSQQRRIRLLSRGPCGSRDPCSNVTCSEFGSTCARSADGLTASCLCPATCRGAPEG  
TVCGSDGADYPGECQLLRRACARQENVFKKFDGPCDPCQALPDPSRSCRNVNPRTRRPEMLLRPESCPARQAPVC  
GDDGVITYENDCVMGRSGAARGLLQKVRSGQCQGRDQCFEPCRFNAVCLSRGRPRCSCDRVTC DGAYRPVCAQD  
GRTYSDSCWRQQAECRQORAIPSKHQGPCDQAPSPCLGVQCAFGATCAVKNGQAACECLQACSSLYDPVCGSDGV  
TYGSACELEATACTLGREIQVARKGPCDRCGQCRFGALCEAETGRCVCPSECVALAQPVCGSDGHTYTPSECMLHV  
HACTHQISLHVASAGPCETCGDAVCAFGAVCSAGQVCPRCEHPPPGFVCGSDGVITYGSACELREAACIQQTQIE  
EARAGPCEQAECGSGSGSGEDGDCEQELCRQGGIWDDESDGPCVCDFFSCQSVPGSPVCGSDGVITYSTECLEK  
KARCESQRGLYVAAQGACRGPTFAFLPPVAPLHCAQTPYGCCQDNITAARGVGLAGCPSACQCNPHGSYGGTCDP  
ATGQCSCRPGVGGRLRCRCEPGFWNFRGIVTDGRSGCTPCSCDPQGA VRDDCEQMTGLCSCKPGVAGPKCGQCPD  
GRALGPAGCEADASAPATCAEMRCEFGARCVEESGSAHCVCPLTCPEANATKVCSDGVITYGNECQLKTIACRQ  
GLQISIQSLGPCQEAVAPSTHPTASVTVTTTGLLLSQALPAPPALPLAPSSTAHSQTTTPPSSRPRTTASVPR  
TTVWPVLTVPPTAPSPAPSLVASAFGESGSTDGSDEELSGDQEASGGGSGGLEPLEGSSVATPGPPVERASCYN  
SALGCCSDGKTPSLDAEGSNCPATKVFQGVLELEGVEGQELFYTPEMADPKSELFGETARSIESTLDDLFNRSDV  
KKDFRSVRLRDLGPGKSVRAIVDVHFDPTTAFRAPDVARALLRQIQVSRRRSLGVRRPLQEHVRFMDFDWFFAFI  
TGATSGAIAAGATARATTASRLPSSAVTPRAPHPSHTSQPVAKTAAAPTTRRPPTAPSRVPGRRFPAPQOPPKP  
CDSQPCFHGGTCQDWALGGGFTCSCPAGRGGAVCEKVLGAPVPAFEGRSFLAFTLRAHYTLRLALEFRALEPQG  
LLLYNGNARGKDFLALALLDGRVQLRFDITGSGPAVLTSAVPVEPGQWHRLELSRHWRRTLSVDGETPVLGESPS  
GTDGLNLDITDLFVGGVPEDQAAVALERTFVGAGLRGCIRLLDVNNQRLELGIGPGAATRGSGVGKCGDHPCLPNP  
CHGGAPCQNLEAGRFHCQCPFGRVGPTCADEKSPQPNPCHGAAPCRVLPPEGGAQCECPLGREGTFCQTASGQDG  
SGPFLADFNGFSHLELRGLHTFARDLGEKMALEVVF LARGPSGLLLYNGQKTDGKGDFVSLALRDRRLEFRYDLG  
KGAAVIRSREPVTLGAWTRVSLERNRKGALRVGDGPRVLGESVPHTVNLNKEPLYVGGAPDFSKLARAAAVSS  
GFDGAIQLVSLGGRQLLTPEHVL RQVDVTSFAGHPCTRASGHPCLNGASCVPREAAVCLCPGGFSGPHCEKGLV  
EKSAGDVDTLAFDGRFTVEYLN AVTESEKALQSNHFELSLRTEATQGLVLWSGKATERADYVALAIVDGHQLQLSY  
NLGSQPVVL RSTVPVNTNRWL RVVAHREQREGSLQVGNEAPVTGSSPLGATQLD TDGALWLGGLPELPVGPALPK  
AYGTGFVGCLRDVVVGRHPLHLL EDAVTKPELRPCPTP

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**FIGURE 6**

ACAGAGACCCCGAGTTCTACAAGTTCTGTCAGGAGAATGACCAGAGCCTGCTAAACTTCAGCGACTCGGACAGCT  
CTGAGGAGGAAGAGGGGCCGTTCCACTCCCCTGCCAGATGTGCTGGAGGAAGCCAGTGAGGAGGAGGATGGAGCGG  
AGGAAGGAGAAGATGGGGACAGAGTCCCCAGAGGGCTGAAGGGGAAGAAGAATTCTGTTCCCTGTGACCGTCGCCA  
TGGTTGAGAGATGGAAGCAGGCAGCAAAGCAACGCCTCACTCCAAAGCTGTTCCATGAAGTGGTACAGCGCTTCC  
GAGCAGCTGTGGCCACCACCCGAGGGGACCAGGAAAGTGCTGAGGCCAACAAATTCAGGTACAGGACAGTGCTG  
CATTCAATGCTCTGGTTACCTTCTGCATCAGAGACCTCATTGGCTGTCTCCAGAAGCTGCTGTTTGAAAGGTGG  
CAAAGGATAGCAGCAGGATGCTGCAGCCGTCCAGCAGCCCGCTCTGGGGGAAGCTTCGTGTGGACATCAAGGCTT  
ACCTGGGCTCGGCCATACAGCTGGTGTCTGTCTGTCGGAGACGACGGTGTGGCGGCCGTGCTGCGGCACATCA  
GCGTGCTGGTGCCCTGCTTCTGACCTTCCCCAAGCAGTGCCGCATGCTGCTCAAGAGAATGGTGATCGTATGGA  
GCACTGGGGAAGAGTCTCTGCGGGTGCTGGCTTTCTGGTCTCAGCAGAGTCTGCCGGCACAAGAAGGACACTT  
TCCTTGGCCCCGTCCTCAAGCAAATGTACATCAGTATGTGAGGAACTGCAAGTTACCTCGCCTGGTGCCCTCC  
CCTTCATCAGTTTTCATGCACTGGACCTTGACGGAGCTGCTGGCCCTGGAGCCGGGTGTGGCCCTACCAGCAGCCT  
TCCTCTACATCCGCCAGCTCGCCATACACCTGCGCAACGCCATGACCACTCGCAAGAAGGAAACATACCAGTCTG  
TGTAACACTGGCAGTATGTGCACTGCCTCTTCCTGTGGTGGCGGGTCTGAGCACTGCGGGCCCCAGCGAAGCCC  
TCCAGCCCTTGGTCTACCCCTTGCCCAAGTCATCATTGGCTGTATCAAGCTCATCCCCACTGCCCGCTTCTACC  
CGCTGCGAATGCACTGCATCCGTGCCCTGACGCTGCTCTCGGGGAGCTCGGGGGCCTTCATCCCGGTGCTGCCTT  
TCATCCTGGAGATGTTCCAGCAGGTCGACTTCAACAGGAAGCCAGGGCGCATGAGCTCCAAGCCCATCAACTTCT  
CCGTGATCCTGAAGCTGTCCAATGTCAACCTGCAGGAGAAGGCGTACCGGGACGGCCTGGTGGAGCAGCTGTACG  
ACCTCACCTTGGAGTACCTGCACAGCCAGGCACACTGCATCGGCTTCCCGGAGCTGGTGTGCTGCTGTGGTCTGC  
AGCTGAAGTCGTTCTCCGGGAGTGCAAGGTGGCCAACTACTGCCGGCAGGTGCAGCAGCTGCTTGGGAAGGTT  
AGGAGAAGCTCGGCATACATCTGCAGCCGCCGCCAGAGGGTTTCTTCGGCGTCTCTGAGCAGCAGGCAGTGGAAG  
CCTGGGAGAAGCTGACCCGGGAAGAGGGGACACCCCTGACCTTGTAAGTACAGCCACTGGCGCAAGCTGCGTGACC  
GGGAGATCCAGCTGGAGATCAGTGGCAAAGAGCGGCTGGAAGACCTGAACCTCCCTGAGATCAAACGAAGGAAGA  
TGGCTGACAGGAAGGATGAGGACAGGAAGCAATTTAAAGACCTCTTTGACCTGAACAGCTCTGAAGAGGACGACA  
CCGAGGGATTCTCGGAGAGAGGGATACTGAGGCCCTGAGCACTCGGCATGGGGTGGAAAGACGATGAAGAGGACG  
AGGAGGAGGGCGAGGAGGACAGCAACTCGGAGGATGGAGACCCAGACGACAGAGGCGGGGCTGGCCCCCTGGGG  
AGCTGCAGCAGCTGGCCCAGGGGCGGAGGACGAGCTGGAGGATCTGCAGCTCTCAGAGGACGACTGAGGCAGCC  
CATCTGGGGGCGCTGTAGGGGCTGCCGGCTGGTGGCCAGTGTTCACCTCCCTGGCAGTCAGGCCTAGAGGCT  
GGCGTCTGTGCACTTGGGGGAGGCAGTAGACACGGGACAGGCTTTATTTATTTATTTTTCAGCATGAAAGACCAAA  
CGTATCGAGAGCTGGGCTGGGCTGGGCTGGTGTGGCTGCTGAAGCCCCACAGCTGTGGGCTGCTGAAGTCAGCTC  
CGCGGGGAGCTGACCCTGACGTCAGCAGACCGAGACCAGTCCAGTTCAGGGGGAGGCCTGCAGGCCCTGGC  
CCCTTCCACCACCTCTGCCCTCCGTCTGCAGACCTCGTCCATCTGCACCAGGCTCTGCCTTCACTCCCCCAAGTC  
TTTGAAAATTTGTTTCTTTCTTTGAAGTCACATTTTCTTTTAAATTTTTTGTGTTTGCATCCGAAACCGAAAGA  
AATAAAGCGGTGGGAGGCAGGGCCATTGTGTTG

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**FIGURE 7**

MAAAGSRKRRLAELTVDEFLASGFDSESESESESENSPQAETREAREAAARSPDKPGGSPSASRRKGRASEHKDQLSR  
LKDRDPEFYKFLQENDQSLLNFSDSDSSEEEEGPFHSLPDVLEEASEEEDGAEEGEDGDRVPRGLKGKKNSVPVT  
VAMVERWKQAAKQRLTPKLFHEVVQAFRAAVATTRGDQESAEANKFQVTDAAFNALVTFCIRDIGCLQKLLFG  
KVAKDSSRMLQPSSSPPLWGKLRVDIKAYLGSAIQLVSCLSETTVLAAVLRHISVLVPCFLTFFPKQCRMLLKRMVI  
VWSTGEESLRVLAFLVLSRVCRHKKDTFLGPVLKQMYITYVRNCKFTSPGALPFISFMQWTLTELLALEPGVAYQ  
HAFLYIRQLAIHLRNAMTTRKKETYQSVYNWQYVHCLFLWCRVLSTAGPSEALQPLVYPLAQVVIIGCIKLIPTAR  
FYPLRMHCIRALTLLSGSSGAFIPVLPPFILEMFQQVDFNRKPGRMSSKPINFSVILKLSNVNLQEKAYRDGLVEQ  
LYDLTLEYLHSQAHCIGFPELVLPVVLQKSFLECKVANYCRQVQQLGKVQENSAYICSRQRVSFGVSEQQA  
VEAWEKLTREEGTPLTLYYSHWRKLRDREIQLEISGKERLEDLNFPEIKRRKMADRKDEDRKQFKDLFDLNSSEE  
DDTEGFSERGILRPLSTRHGVEDDEEDEEEGEEDSSNSSEDGDPDAEAGLAPGELQQLAQGPEDLEDLQLSEDD